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CHILDREN'S ONCOLOGY GROUP

ALTE1621

Pharmacologic Reversal of Ventricular Remodeling in Childhood Cancer Survivors at Risk for Heart Failure (PREVENT-HF): A Phase 2b Randomized Placebo-Controlled (Carvedilol) Trial

A Groupwide Study

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AGENT
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LIST OF ABBREVIATIONS

A-HF	Anthracycline-induced heart failure
AE	Adverse event
AHA/ACC	American Heart Association/American College of Cardiology
ANP	Atrial natriuretic peptide
BID	Twice daily
BNP	B-type natriuretic peptide
BPM	Beats per minute
CAD	Coronary artery disease
CARMEN trial	Carvedilol ACE inhibitor Remodeling Mild Heart Failure Evaluation trial
CHOA	Children's Healthcare of Atlanta
COG	Children's Oncology Group
CPIR	Consortium for Pediatric Interventional Research
CTCAE	Common Terminology Criteria for Adverse Events
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CV	Cardiovascular
DMD	Duchenne muscular dystrophy
E/A ratio	Peak early atrial divided by peak late atrial velocities
EF	Ejection fraction
ESWS	End-systolic wall stress
ET	Ejection time
HD	High-dose
HF	Heart failure
HRQL	Health-related quality of life
HSC/SickKids	Hospital for Sick Children
IVCT	Isovolumetric contraction time
IVRT	Isovolumetric relaxation time
LTFC	Long-Term Follow-up Clinic
LV	Left ventricular
LVEDD	LV end-diastolic dimension
LVEDV	LV end-diastolic volume
LVESD	LV end-systolic dimension
LVESV	LV end-systolic volume
LVESVI	LV end-systolic volume index
LV P	LV pressure
LVPWD	LV posterior wall thickness at end-diastole
LVPWS	LV posterior wall thickness at end-systole
LV T	LV thickness
LV T-D	LV posterior wall thickness-dimension ratio
LV V	LV volume
MCI	Myocardial contractility index
MPI	Myocardial performance index
MUCHA trial	Multicenter Carvedilol Heart Failure Dose Assessment trial

MV	Mitral valve
NT-Pro-BNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PMH	Princess Margaret Hospital
QD	Once daily
SAVE trial	Survival and Ventricular Enlargement trial
SF	Shortening fraction
SJCRH	St. Jude Children's Research Hospital
SNPs	Single nucleotide polymorphisms
SOLVD-P	Study of Left Ventricular Dysfunction-Prevention
UM	University of Michigan
UMCCC	University of Michigan Comprehensive Cancer Center
WCI	Winship Cancer Institute
WMSI	Wall motion score index

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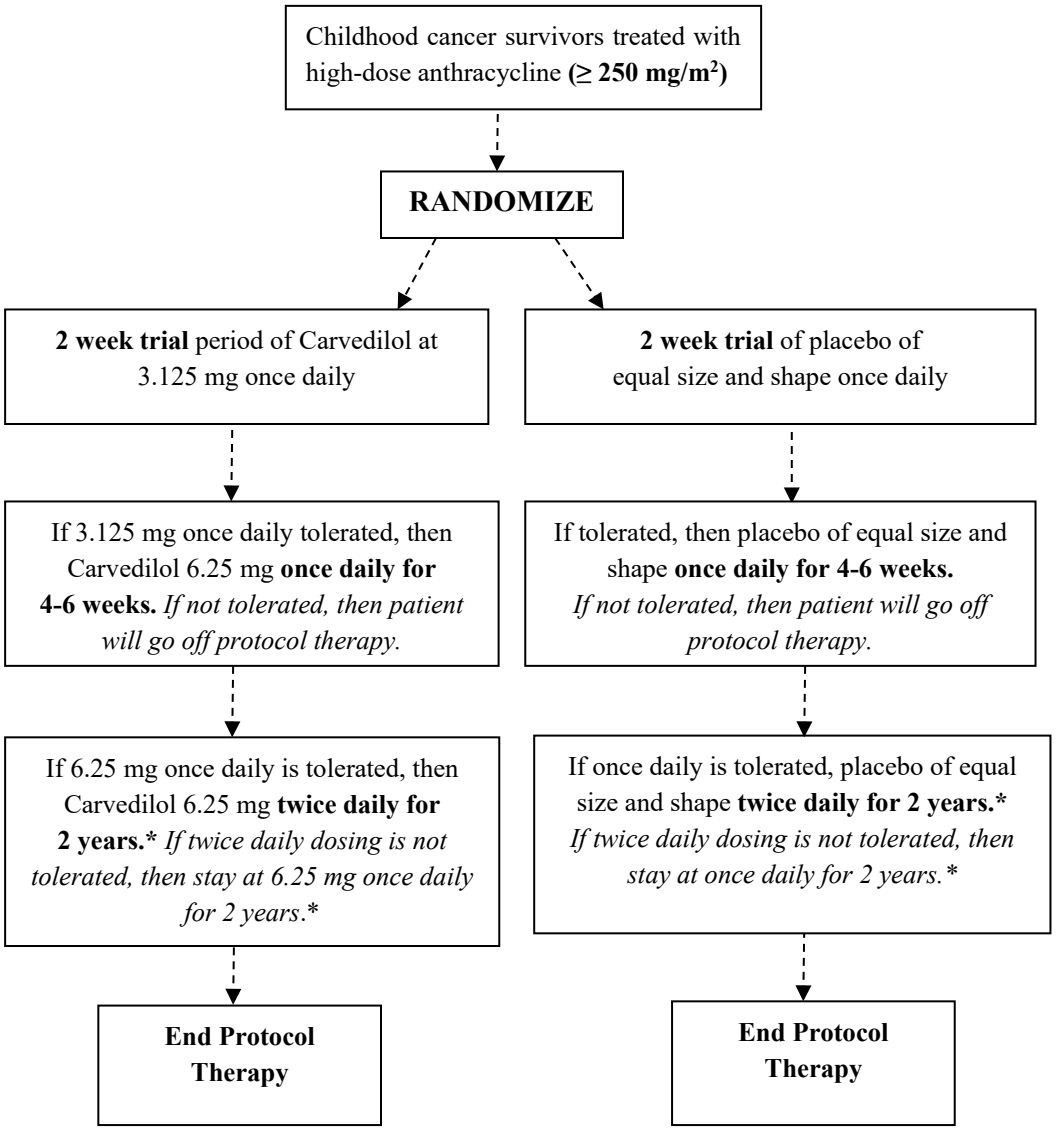
ABSTRACT

Heart failure [HF], is one of the leading causes of late morbidity and premature death after successful treatment of childhood cancer with anthracycline chemotherapy.[1-4] In fact, childhood cancer survivors are at a 15-fold increased risk of developing HF compared to age-matched healthy controls.[5] The risk is higher among those exposed to anthracyclines at a young age, and among those with concomitant exposure to chest radiation.[6-9] This anthracycline-related cardiotoxicity presents as a continuum from asymptomatic structural or functional cardiac abnormalities detected on imaging studies, to clinically symptomatic HF.[10-12] There is a strong dose-dependent relationship between anthracycline chemotherapy exposure and HF risk. Anthracycline-related cardiotoxicity is dose-dependent: the incidence of A-HF is < 5% with cumulative anthracyclines exposure of < 250 mg/m²; the incidence approaches 15% at doses between 250 and 500 mg/m²; and exceeds 30% for doses > 600 mg/m².[1,6,8-10] Outcome following anthracycline-related HF is poor; 5-year overall survival rate is < 50%.[13,14] Nearly 60% of all childhood cancer survivors carry a history of prior anthracycline exposure.[9,15] The decades of life saved among the rapidly growing anthracycline-exposed childhood cancer survivors, makes it imperative that we develop strategies (informed by the pathogenic basis of anthracycline-related cardiotoxicity) to reduce the risk of HF in the vulnerable populations.[16,17]

Anthracycline cardiotoxicity results from direct cardiac injury due to formation of free radicals; this injury initiates cardiac remodeling and subsequent deterioration of left ventricular (LV) function. β-blockade or angiotensin-converting enzyme (ACE)-inhibition have been successfully used to prevent HF in adult non-oncology populations with asymptomatic LV dysfunction,[18-20] as well as in pediatric non-oncology populations with genetic predisposition to HF (but with preserved cardiac function at the time of intervention).[21] There is increasing evidence supporting a comprehensive reversal of parameters used to measure cardiac remodeling, with the use of third generation β-blockers such as carvedilol (combined β1, β 2, α1 blockade) when compared with ACE inhibitors (afterload reduction alone) following exposure to cardiotoxic agents (such as HD-anthracyclines).[4,17,20] However, despite clear physiologic rationale, as well as evidence of clinical efficacy in non-oncology populations, clinicians are reluctant to use pharmacologic intervention in childhood cancer survivors, primarily due to a paucity of randomized clinical trials that would provide evidence for benefit from such an intervention.[22,23] We address this gap in the proposed trial: a randomized, double-blind, placebo-controlled Phase 2b trial in asymptomatic childhood cancer survivors with prior exposure to HD-anthracyclines (≥ 250 mg/m^2).

This study will provide critical information regarding a physiologically plausible pharmacological risk-reduction strategy for childhood cancer survivors at high risk for developing anthracycline-related HF. The proposed intervention has the potential to significantly reduce ongoing cardiac injury via interruption of neuro-hormonal systems responsible for LV remodeling, resulting in improved cardiac function and decreased risk of HF. The intervention is informed by previous studies demonstrating efficacy in pediatric and adult non-oncology populations, yet remains unstudied in the pediatric oncology population. The intervention will rely on reproducible and clinically relevant echocardiographic and blood biomarkers of early cardiac remodeling. Finally, the proposal leverages the well-established clinical trials network of the Children's Oncology Group (COG), allowing participation by geographically diverse patient populations.

EXPERIMENTAL DESIGN SCHEMA



* Carvedilol or placebo will be administered for a total of 2 years, beginning with the first dose of study drug.

The primary endpoint is left ventricular posterior wall thickness to dimension ratio, which will be measured at baseline and on a semi-annual basis.

Blood draws will be scheduled semi-annually for measurement of circulating markers of efficacy and safety. A complete list of required observations can be found in Section 7.1.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aim

To determine the impact of a two-year course of low-dose carvedilol on surrogate echocardiographic indices of heart failure (HF) risk, including:

- Left Ventricular (LV) Posterior Wall Thickness-Dimension Ratio (LV T-D) a well-established index of early myocardial remodeling and subsequent HF risk (primary endpoint).
- LV Systolic and Diastolic Function, and Afterload – established echocardiographic indices associated with HF risk.
- Natriuretic Peptides, Troponins, and Galectin-3 – circulating biomarkers associated with myocardial injury, and HF risk.

1.2 Secondary Aims

1.2.1 To establish safety and tolerability of this two-year course of low-dose carvedilol, assessing both objective measures (hepatic function) and patient reported outcomes**.**

1.2.2 To examine the modifying effect of demographic, clinical, and molecular characteristics on the risk: benefit ratio from this two-year carvedilol intervention.

1.3 Exploratory Aim

To evaluate the long-term efficacy of carvedilol in preventing cardiomyopathy and/or heart failure in high-risk childhood cancer survivors.

2.0 BACKGROUND AND HYPOTHESES

2.1 Risk of HF in Childhood Cancer Survivors

Anthracyclines (doxorubicin, daunomycin, idarubicin and mitoxantrone) are widely used in the treatment of childhood cancer; the use of these agents has led to significant advances in the outcome of many childhood cancers;[2] current 5-year survival rates approach 80%.[24] Clinically, one of the most widely recognized side-effects of anthracycline therapy is dose-dependent cardiotoxicity, manifesting as a continuum from asymptomatic cardiac dysfunction identified by abnormalities of cardiac function/structure on imaging studies, to the clinically overt heart failure.[2] Outcome following diagnosis of anthracycline-induced heart failure (A-HF) is generally poor, with overall survival of less than 50% at 5 years.[22,25] Current estimates indicate that nearly 60% of the 400,000[26] survivors of childhood cancer in the U.S. will have been treated with anthracyclines[7,8] – a vulnerable sub-population at risk for symptomatic heart disease, and therefore representing a critical need for interventions to decrease/reverse this morbidity.[9,12]

2.1.1 Magnitude of Risk of A-HF

Childhood cancer survivors are at a 15-fold increased risk of developing A-HF, and at a 7-fold increased risk of dying from a cardiac cause, compared with age- and sex-matched general population.[1,27] Survivors of Hodgkin lymphoma, renal tumor and Ewing sarcoma are at a 12 to 13-fold increased risk of cardiac death. Finally, the risk of dying from cardiac causes increases with time from diagnosis of primary cancer.[27] Thus, it is abundantly clear that anthracycline-related cardiac morbidity and mortality is significantly elevated in long-term survivors of childhood cancer.

2.1.2 Risk Modification by Anthracycline Dose, Length of Follow-up, and Age at Exposure

Individuals treated with anthracyclines at a younger age (< 5 years) are at an increased risk of A-HF, in part, because of cardiotoxic insult to a growing myocardium.[28] Younger age at diagnosis is associated with severity of LV myocardial thinning, and abnormal cardiac contractility.[29,30] Radiation therapy involving the heart is known to damage the myocardium by injuring capillary endothelial cells, which causes obstruction of the capillary lumen, formation of platelet and fibrin thrombi, and subsequent myocyte death.[6] Over time, this process leads to myocardial fibrosis and restrictive cardiomyopathy that is characterized by combined diastolic and systolic dysfunction.[6,31] Childhood cancer survivors exposed to both anthracyclines and chest radiation have a significantly increased risk of developing A-HF when compared to those treated with either therapeutic approach alone, and the risk continues to increase with longer follow-up.[23,28,32]

Anthracycline-related cardiotoxicity is dose-dependent: the incidence of A-HF is < 5% with cumulative anthracycline exposure of < 250 mg/m²; the incidence approaches 15% at doses between 250 and 500 mg/m²; and exceeds 30% for doses > 600 mg/m².[1,6,8-10] A recent report[27] found the adjusted risk of A-HF after exposure to > 250 mg/m^2 to be 13-fold (Odds Ratio [OR]=13.3, $p < 0.01$) higher than those not exposed to anthracyclines; the risk was nearly 6-fold (OR=5.7, $p < 0.01$) higher for individuals exposed to high-dose anthracyclines, when compared to < 250 mg/m². Similarly, other reports,[28-31] indicate the risk of A-HF to be greatest for survivors treated with cumulative doses ≥ 250 mg/m²; and have also demonstrated that the risk of A-HF for survivors exposed to < 250 mg/m^2 was equivalent to those with no exposure; the incidence of cardiac abnormalities continues to increase with longer follow-up.[6,28,29,32,33] These studies suggest that childhood cancer survivors treated with cumulative anthracycline doses exceeding 250 mg/m² are at a significantly higher risk of developing A-HF.

2.1.3 Natural History of Cardiotoxicity

The American College of Cardiology/American Heart Association (ACC/AHA) 2005 guidelines for the diagnosis and management of heart failure (HF) describe HF as a progressive disorder (Figure 1).[18]

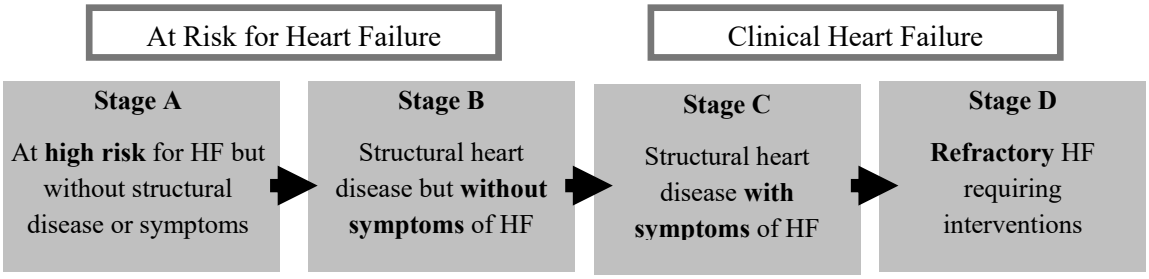


Figure 1: ACC/AHA Guidelines

LV dysfunction begins with some injury to, or stress on, the myocardium (Stage A) and is progressive even in the absence of a new identifiable insult to the heart. The eventual manifestation is a change in the geometry or structure of the left ventricle (Stage B) which precedes clinically overt signs and symptoms (Stage C). If left untreated or if the cardiac injury is too severe, an individual will progress to

refractory disease (Stage D). According to the ACC/AHA guidelines, patients either remain in their current stage or advance from one stage to the next, but do not revert back to an earlier stage. It is well-recognized that there is a long latency between asymptomatic (Stage A/B) and clinically evident (Stage C/D) disease. Over time, anthracycline exposure leads to a decrease in LV wall thickness, increase in LV dimension, and subsequent increase in LV end-systolic wall stress (ESWS) – a critical component of the neuro-hormonal imbalance and a well-recognized precursor to A-HF.[6,16,34] In survivors treated with high-doses of anthracyclines, nearly 60% of asymptomatic individuals have markedly abnormal indices of myocardial remodeling, with a clear dose-response relationship with anthracyclines.[16,35-38]

Once an individual develops A-HF, the overall survival is less than 50% at 5 years from diagnosis.[7,22,23] The poor outcome highlights the importance of early intervention strategies for the prevention of A-HF in childhood cancer survivors.

2.2 Mechanism of Anthracycline-Related HF

Anthracycline cardiotoxicity is thought to be related to direct myocardial injury due to formation of free radicals.[10] Reactive oxygen species can be generated by a variety of pathways including redox cycling, iron complexation, and disruption of the electron transport chain.[39-41] Anthracyclines can also alter antioxidant defense systems and DNA repair pathways.[42,43] The subsequent effect on the myocardium may include: damage to nuclear DNA, disruption of sarcomeric proteins, changes in calcium handling and cellular contractility, and suppression of transcription factors that regulate cell survival and sarcomeric protein synthesis.[11,13,14] If enough myocardial injury occurs, the heart expands in size and the chamber walls become thinner, creating a clinical picture similar to dilated cardiomyopathy.[6]

Once the myocardium has been damaged by anthracyclines, changes in contractility ensue over time, resulting in increased renin activity, followed by increase in afterload, and sympathetic activation.[9,15,16] The compensatory increases in afterload and sympathetic activation are mediated by β1, β2, and α1 receptors as well as the renin-angiotensin system. Chronic activation of all three sympathetic pathways (β1, β2, α1) further worsens myocardial injury which, over time, leads to myocardial decompensation and clinical HF.[17,19,20] The characteristically delayed manifestation of symptomatic cardiotoxicity after anthracycline exposure is likely related to the eventual failure of a reduced number of cardiomyocytes in response to the increase in afterload and/or sympathetic activation.[2,16] Blockade of these pathways relatively soon after anthracycline exposure, by using a third generation β–blocker such as carvedilol in prevention of A-HF holds considerable appeal, and is discussed in Section 2.3.6.

2.3 Current Options for HF Risk Reduction

For non-oncology populations (prior myocardial infarction, or idiopathic LV dilatation and hypokinesia), there is universal agreement about the importance of instituting appropriate pharmacologic intervention in at risk patients as soon as possible, and definitely before the onset of heart failure.[18,19]

2.3.1 Treatment Strategies in Adults at High Risk for HF

The largest trials to date in the treatment of Stage B (asymptomatic) disease are the Study of Left Ventricular Dysfunction-Prevention (SOLVD-P) and the Survival and Ventricular Enlargement (SAVE) trial.[44] The SOLVD-P trial enrolled

4,228 asymptomatic or mildly symptomatic patients with reduced ejection fraction (EF), who were assigned to receive either placebo or ACE-inhibitor, enalapril for 48 months. After follow-up of 37 months, patients receiving enalapril showed a trend toward increased survival and a significant reduction in the risk of development of clinical heart failure.[44] A subsequent extended follow-up study (12 years) of patients enrolled in the SOLVD-P trial showed that the survival benefit in the enalapril arm persisted long past trial termination, suggesting that the preventive effects of ACE-inhibition likely continue, in part, because of the early intervention.[45] The SAVE trial enrolled 2,231 patients after myocardial infarction, with asymptomatic LV dysfunction (ACC/AHA classification: Group B), who were assigned to placebo or a different ACE-inhibitor, captopril. After a follow-up of 42 months, a significant reduction of both mortality (19%) and hospitalization for heart failure (22%) was observed.[44] These results in asymptomatic or nearly asymptomatic patients, together with subsequent studies,[20,46,47] validated the paradigm of neuro-hormonal antagonism for heart failure prevention. As a result, there has been a shift in therapeutic intent from management of symptoms to addressing pathophysiology.[18-20,46]

2.3.2 Beta Blockers in at Risk Adult Populations

It is increasingly recognized that maladaptive sympathetic activation continues in patients with asymptomatic LV dysfunction despite treatment with ACE inhibitors. In post-hoc analyses of the SOLVD-P[48] and SAVE[49] trials, it was evident that those who received β-blockade in addition to afterload reduction had significantly improved overall outcomes when compared to those not receiving β-blockers. In addition, patients with non-ischemic cardiomyopathy did not appear to derive the same clinical benefit from ACE-inhibitors as the patients with ischemic cardiomyopathy.

More recently, the Carvedilol ACE inhibitor Remodeling Mild Heart Failure Evaluation (CARMEN) trial[47] randomized participants with mild heart failure to: enalapril (ACE-inhibition), carvedilol (combined β1-2, α1 blockade), or both. LV remodeling was assessed by serial LV end-systolic volume index (LVESVI) measurements for 18 months. Carvedilol significantly reduced LVESVI ($p < 0.01$) compared to baseline, whereas enalapril did not. All study arms showed similar safety profiles and withdrawal rates. As a result, it was concluded that while enalapril alone may have attenuated further myocardial remodeling, carvedilol *reversed* the process, resulting in greater decrease in LVESVI and improvement in EF. This improvement in outcome was attributed to concurrent afterload reduction (α1-blockade) and blockade of adrenergic activation (combined β1-2) provided by carvedilol. The findings from the CARMEN study reinforce the importance of early, comprehensive (combined β1-2, α1 blockade as offered by carvedilol), intervention for reversal of myocardial remodeling and neuro-hormonal imbalance in populations at risk for HF.

2.3.3 Beta Blockers in Pediatric Population

Several studies have evaluated the efficacy and safety of β-blockers in children with idiopathic dilated cardiomyopathy, muscular dystrophy, or congenital heart disease.[50-57] Carvedilol has been the most frequently utilized drug due to its favorable safety profile and broad multi-receptor blockade.

The studies by Azeka[52] and Shaddy[55] compared safety and tolerability of carvedilol using a randomized, placebo-controlled study design; the frequency of adverse events (hypotension, dizziness, fatigue and weakness) or withdrawal rates were equivalent between the two arms. The severity of symptoms correlated with severity of heart failure, a finding also reported in several large adult trials.[17] Information regarding safety and tolerability of carvedilol in children with asymptomatic disease is scarce, but it would follow from the reports above that both the frequency and severity of adverse events would be fewer among patients with asymptomatic disease. Two single-arm studies[57,58] in children and adolescents with mild dilated cardiomyopathy due to muscular dystrophy reported no adverse events which necessitated dose reduction or drug discontinuation. These studies illustrate the following: 1) carvedilol is an efficacious option for reversal of cardiac dysfunction in at-risk children and adolescents with non-ischemic cardiomyopathy; 2) in the setting of mild HF or asymptomatic disease, low-dose carvedilol is a safe and well-tolerated therapeutic option for HF risk reduction.

2.3.4 Secondary Pharmacologic Intervention in Pediatric Patients at High Risk for HF

Duchenne muscular dystrophy (DMD) is characterized by progressive muscle weakness and eventual cardiac involvement. Much like A-HF, cardiac involvement begins as minor electrocardiographic abnormalities at a young age, evolves toward cardiomyopathy with dilation of cardiac chambers and subsequent decrease in LV EF. Most develop refractory dilated cardiomyopathy, which is responsible for nearly 50% of patient deaths.

Treatment with ACE-inhibitors or β-blockers has been shown to improve cardiac function among patients with Stage C disease and delay onset of refractory (Stage D) disease.[59] However, few have lasting improvement in outcomes. Most patients develop progressive disease despite pharmacologic intervention due, in part, to the prolonged myocardial remodeling and neuro-hormonal imbalance which precedes clinically overt disease. The only secondary prevention trial randomized children with DMD (range 9.5 – 13 years old) with preserved EF to afterload reduction *v* placebo.[60] Median EF at study entry was 65.0% ± 5.5% and none had clinical evidence of HF. In this double-blinded, multi-center trial, overall survival in the intervention arm was significantly superior to placebo at 10 years (93% *v* 65.5%). All deaths were due to cardiopulmonary failure. This study was one of the first to demonstrate the critical importance of intervention prior to onset of clinically evident disease in patients with preserved EF, but known to be at high risk for developing HF, a strategy advocated in the current protocol.

2.3.5 Pharmacologic Intervention for Survivors of Childhood Cancer at Risk for A-HF

Clinicians caring for childhood cancer survivors have been hesitant to use secondary pharmacologic intervention strategies (either ACE-inhibitors or β-blockers) in asymptomatic at risk populations, in large part because of the paucity of well-conducted randomized interventional clinical trials that would provide the evidence for such an intervention.[61,62]

A retrospective review of 18 doxorubicin-exposed survivors of childhood cancer revealed that treatment with enalapril for a median of 10 years was associated with improvement in LV dimension, afterload, and shortening fraction (SF) in all patients.[61] However, the beneficial effects appeared to be transient. The 6 patients with symptomatic disease progressed to cardiac transplantation or death,

reinforcing the previously reported poor outcomes when intervention is initiated after onset of clinically symptomatic disease. Of the 12 patients with asymptomatic disease, 3 developed heart failure or died. However, due to the relatively small number of asymptomatic individuals included in the study as well as to the non-randomized nature of the intervention, it was unclear what effect, if any, ACE-inhibition played in the prevention of progression to clinical HF.

The only randomized clinical trial of afterload reduction (α1-blockade with ACE inhibitors) in asymptomatic survivors exposed to any dose of anthracyclines conducted thus far,[62] failed to demonstrate a clinically detectable difference in the primary endpoint (myocardial contractility index [MCI]). However, there was significant reduction in ESWS that persisted over the study period. More importantly, there were seven individuals who were taken off study due to deterioration in cardiac function. Six of seven (86%) had been randomly assigned to placebo, and one had been randomized to ACE inhibitors ($p = 0.06$). All but one in the placebo arm who developed progressive dysfunction had received high-dose anthracyclines. The one individual randomized to the intervention arm was receiving concurrent growth hormone replacement (reported by some to exacerbate progression of cardiac dysfunction). Due to small numbers, the investigators were unable to make recommendations regarding secondary pharmacologic intervention.

2.3.6 ACE-inhibitors v β-blockers for Prevention of A-HF in Childhood Cancer Survivors

As detailed in Section 2.2, injury to the myocardium results in activation of α1 and β1,2 receptors, and neurohormonal overstimulation. Myocardial loss occurs by adrenergically-mediated acceleration of apoptosis, increase in myocardial oxygen consumption, and wall stress, with subsequent fibrosis and worsening cardiac function.[57] As a result, individuals with asymptomatic LV dysfunction treated with ACE-inhibitors alone (selective α1-like blockade) would continue to have adrenergic stimulation of the myocardium.[48,49] Over time, this chronic stimulation could worsen myocardial injury and further compromise contractility. Third generation beta-blockers such as carvedilol have been shown to *reverse* myocardial remodeling via combined α1 and β1,2 receptor blockade,[47] making carvedilol a more efficacious option for childhood cancer survivors at high risk for A-HF. Carvedilol is well-tolerated in children and adolescents with clinical HF, and has a more favorable safety profile when compared to ACE-inhibitors. Currently, there is a U.S. boxed warning against the use of enalapril, an ACE-inhibitor, in women who are pregnant or planning on becoming pregnant, because it can cause injury and death to the developing fetus when used in the second and third trimesters.[63] Carvedilol is a pregnancy category C drug, and the potential benefits may warrant use of the drug in pregnant women despite potential risks. The current trial will not include individuals who are pregnant or planning on becoming pregnant. However, we believe the more favorable risk profile of carvedilol adds additional weight to the choice of carvedilol over enalapril in the preventive care setting.

Thus, with regards to A-HF, the following issues are clear:

i) Children exposed to ≥ 250 mg/m^2 are at high risk of developing cardiomyopathy;
ii) If left unattended, asymptomatic cardiomyopathy (Stage B) often progresses to A-HF;
iii) A-HF is associated with poor survival;
iv) There is a need for a comprehensive intervention approach to halt and reverse the anthracycline-related cardiac damage relatively early in its course in order to prevent the progression to A-HF;
v) Studies in non-oncology populations have demonstrated safe and effective options for secondary pharmacologic intervention. However, there remains a gap in knowledge regarding the preventive strategies in anthracycline-exposed survivors.

The current study will address these gaps in knowledge by evaluating the benefit of pharmacologic intervention targeted to survivors at *highest risk* for A-HF. We believe, that the proposed intervention with carvedilol will provide a more comprehensive reversal of myocardial remodeling through concurrent sympathetic inactivation (β1,2-blockade) and afterload reduction (α1-blockade), increasing the likelihood of clinically significant risk reduction.

2.4 Early markers of HF risk reduction

One of the recognized challenges to conducting clinical trials that evaluate secondary prevention strategies is the long latency between asymptomatic and clinically overt disease.[6,12,16,64] Prevention trials focusing on cardiovascular disease have increasingly relied on surrogate endpoints for assessment of response to an intervention.[34,61,62,65,66] While blood biomarkers exist, most evaluations are based on serial echocardiographic measurements of early myocardial remodeling.

2.4.1 Blood Biomarkers

Troponin, a thin-filament-associated complex regulating the formation of actin-myosin cross bridges in striated muscle, consists of three subunits: troponin T, C, and I.[67] Cardiac troponins T (cTnT) and I (cTnI) are specific and sensitive biomarkers for myocardial cell injury, and have established diagnostic and prognostic value in acute coronary syndrome and other forms of myocardial injury.[67,68] cTn's have successfully been used as biomarkers to monitor acute anthracycline-related cardiotoxicity.[69-72] However, little is known regarding their utility for diagnosis and monitoring of long-term chronic cardiac injury or response to pharmacotherapy.[67] cTn levels have failed to identify mild heart dysfunction in patients followed long-term,[73-75] arguing against their use as a biomarker of response to pharmacologic intervention.

Natriuretic peptides (NP) are hormones produced in the atrium (ANP) and ventricle (NT-Pro-BNP, BNP) in response to myocardial wall stress.[76,77] They act as potent natriuretics and vasorelaxants to improve myocardial performance, and have become established biomarkers for the diagnosis of heart failure.[77] NPs serve as independent risk factors for adverse cardiovascular events, and are being increasingly advocated as objective markers to monitor and adjust anti-congestive treatment.[78,79] However, there are limitations to their widespread use due to their low specificity and wide variability in the measured value, determined both by the

specific peptide assay as well as by physiologic conditions.[67,80] Compared to cTn, clinical studies have been more consistent regarding the diagnostic value of NPs in A-HF monitoring.[67] Several studies have documented that BNP levels, if persistently elevated, correlate well with echocardiographic indices of myocardial dysfunction.[81-83] Due to wide inter-patient variability of NP values in individuals with asymptomatic LV dysfunction, the establishment of an appropriate cutoff for therapeutic response measurement is difficult.

Most biomarkers such as troponin and BNP are released into the circulation as a result of harmful cellular processes, and therefore represent 'bystander' biomarkers. Galectin-3, a protein produced by activated macrophages, is a member of a family of β-galactoside-binding lectins and promotes cardiac fibroblast proliferation and collagen synthesis following myocardial injury; [84,85] inhibition of galectin-3 appears to block or reverse the process.[86] As a result, galectin-3 is considered a 'culprit' biomarker, analogous to viral load, low-density lipoprotein, and glucose.[85] Increased myocardial expression of galectin-3 is seen during early stages in myocardial remodeling and may help identify individuals with preclinical risk factors who are more likely to develop overt heart failure.[87] Serial measurement of Galectin-3 may be helpful for monitoring of response to pharmacologic intervention. **Whether serial blood biomarker measurements could be useful for evaluation of response to pharmacologic intervention remains to be defined;** currently, the use of biomarkers in the management of heart failure remains a Class III recommendation.[88] The current trial will afford us the ability to evaluate: i) whether changes in biomarkers correlate with corresponding changes in echocardiographic indices; and ii) the independent role of specific biomarkers as surrogates in predicting the risk of progressive disease.

2.4.2 Echocardiographic Detection of Myocardial Dysfunction

Traditionally, the detection of late-occurring anthracycline-related cardiotoxicity has relied upon serial screening of at risk survivors using resting EF and SF.[89] These parameters have increasingly been recognized as inadequate for detecting subtle changes in myocardial function.[90,91] Myocardial biopsy studies have demonstrated that myocyte dysregulation and apoptosis occur years prior to changes in EF, and a significant proportion of the myocardium would have to be damaged to exceed the threshold for detection.[90,92,93] Often, at the point when changes in EF or SF are detected, functional deterioration proceeds rapidly and is mostly irreversible. The limitations of relying on changes in LV EF to intervene are further compounded by the knowledge that among the non-oncology populations, nearly half of all heart failure occurs in patients who maintain a normal EF,[90,94,95] emphasizing the need for echocardiographic indices that detect changes at an earlier stage in myocardial compromise, as described below.

Anthracycline exposure over time leads to a decrease in LV wall thickness and increase in LV end-diastolic dimension (LVEDD), resulting in decreased LV thickness dimension ratio (LV T-D). The decreased LV T-D and concurrent increase in LV end-systolic wall stress (ESWS) is a well-recognized precursor A-HF.[6,16,34]

Left ventricular thickness-dimension ratio (LV T-D) is a well-established load-independent composite echocardiographic parameter of myocardial remodeling, and takes into consideration changes in LVEDD and LV wall thickness, over time. Among survivors exposed to high-dose anthracyclines, LV T-D is expected to

decrease with follow-up, despite relative preservation of global LV systolic function, as measured by EF and SF. [6,16,21] Thus, decrease in LV T-D is a critical component of the neuro-hormonal imbalance and is a well-recognized early precursor to A-HF.[6,16,34] Furthermore, LV T-D has been reliably used as an endpoint in other chemoprevention trials in both oncology and non-oncology populations.[15,57,61,62] **As a result, LV thickness-dimension ratio will serve as the *primary endpoint* in the current study.**

Left ventricular end-systolic wall stress (ESWS) is an echocardiographic measure of LV afterload and is derived from La Place's law describing the relationship between LV pressure (P), volume (V), and wall thickness (T): Wall stress α (P x V)/T.[15] For survivors treated with high-dose anthracyclines, decrease in LV thickness (T), and increase in LV volume (V), results in increased ESWS. Similar to LV T-D, ESWS continues to increase over time, despite normal- to reduced blood pressure, due to decreased LV thickness and mass. Studies have shown that pharmacologic intervention with afterload reduction can improve ESWS in asymptomatic survivors.[61,62] It remains to be seen if this decrease in ESWS can provide effective and lasting reversal of myocardial remodeling, as measured by LV T-D. In the current trial, ESWS will serve as a *secondary endpoint*.

Myocardial performance index (MPI)[49] is a Doppler-derived parameter that provides global assessment of systolic and diastolic function. MPI is defined as the ratio of the sum of isovolumic relation time and isovolumic contraction time, to the ejection time – all parameters that can be obtained from routine Doppler imaging studies. MPI is attractive as an echocardiographic index because it is independent of heart rate and blood pressure; provides information regarding diastolic and systolic function; is load independent; does not rely on geometric assumptions about ventricular shape; and is highly reproducible in adult non-oncology populations at risk for HF.[96,97] MPI has been shown to be predictive of HF in a cohort of elderly men who had not yet developed LV dysfunction[98] and in predicting clinical response to medical treatment for individuals with both systolic heart failure and heart failure with preserved EF.[99] Preliminary studies in childhood cancer survivors treated with anthracyclines have shown MPI to be a useful pre-clinical marker of myocardial dysfunction;[100-102] larger studies are needed to evaluate the utility of MPI for routine screening and management of myocardial dysfunction in childhood cancer survivors. In the current trial, MPI will serve as a *secondary endpoint*.

Several studies evaluating early changes in cardiac function during and after anthracycline treatment have noted primarily diastolic impairment which precedes systolic dysfunction.[101,103] Commonly used LV diastolic measurements include: mitral inflow E/A ratio (peak early atrial divided by peak late atrial velocities), and isovolumic relaxation time (IVRT) – interval between aortic valve closure and mitral valve opening, and a component of MPI.[103] Reduction in E/A ratio in the absence of systolic dysfunction is often observed in long-term survivors treated with anthracyclines. [101,103] However, the predictive value of this and other diastolic parameters is not yet known. Other echocardiographic measurements of early myocardial dysfunction include: changes in end-diastolic and systolic diameters (LVEDD, LVESD), decrease in *systolic* LV posterior wall thickness (LVPWS), increase in wall motion score index (WMSI), and decrease in LV mass.[2,16,104] These indices will be included as *secondary endpoints* in the current trial.

Electrocardiograms (ECG) are readily available and noninvasive, but lack sensitivity in detecting anthracycline-related cardiotoxicity and do not measure LV function. Previous studies have suggested that prolongation of the QTc interval may be useful in early detection of anthracycline-induced subclinical cardiotoxicity and a marker of overall cardiac health.[38,83,105] However, changes in QTc interval are non-specific and there is low correlation between electrocardiographic changes and the morphologic or clinical findings of anthracycline cardiomyopathy.[28] Because of the lack of sensitivity or specificity, ECG will not be considered as a biomarker for detection of anthracycline-related cardiotoxicity; however, ECG will be routinely monitored during the trial to assess the safety of the pharmacologic intervention.

2.5 Pharmacogenetics

There is widespread recognition that despite the beneficial effect of β-blockers in the prevention of HF, there remains significant inter-patient variability in drug response,[106,107] suggesting the role of genetic susceptibility in the response to β-blockers. Genetic polymorphisms affecting proteins in the adrenergic receptor pathways as well as drug metabolism have been identified as modifiers of β-blocker response and heart failure risk.[106-110] As a result, clinical trials have increasingly relied on pharmacogenetics to evaluate sub-populations which may derive most benefit from an intervention.[111-113]

Twenty-six β1-receptor and 20 β2-receptor single nucleotide polymorphisms (SNPs) have been described, but only two variants of each receptor are common and extensively studied with respect to carvedilol response and cardiovascular function.[109,114,115] Polymorphisms in other adrenergic receptors (α2c-AR) and the norepinephrine transporter[108] may further modulate pharmacologic response via alteration of pre-synaptic norepinephrine re-uptake and transport.[108,111,116] On the other hand, polymorphisms in genes involved in beta blocker metabolism (CYP2D6) may modulate the dose required for a desired therapeutic response.[110] Table 1 details specific SNPs that have been identified as candidate genetic modifiers and will be included in the current clinical trial. These polymorphisms were selected based on the following concepts: i) a candidate gene approach will be used; ii) functional polymorphisms will be evaluated; iii) genes will be identified by virtue of the fact that they have been previously documented as modifiers of carvedilol response or clinical course of HF.

Table 1. Candidate genes with a potential role in modifying carvedilol response

Gene, polymorphism, and allelic frequency (AF)	Function	Functional change (in vitro)	Genotype/phenotype associations
β 1-Adr. receptor (β1-AR) - Ser49Gly, AF: 0.12-0.28 - Arg389Gly, AF: 0.20-0.46	↑CO: ↑HR, ↑impulse conduction, contraction increased LV volume β_1-AR down-regulated in chronic HF.	Ser49>Gly: resistance against desensitization[106] Arg→Gly: ↓responsiveness to agonist stimulation[106]	DCM: Gly49 allele lower risk of death or cardiac transplant.[117] Carvedilol: Arg389-homozygous improved LVEF *v* Gly-389 homozygous[114]
β 2-Adr. receptor (β2-AR) - Gln27Glu, AF: 0.39-0.51 - Arg16Gly, AF: 0.09-0.25	Cardiac: similar activity as β1-AR; relative up-regulation in HF.	Alter extent to which receptors undergo downregulation.[106]	Carvedilol: Glu27 carriers w/HF improved LVEF (62% of cases) compared to Gln homozygous (26% of cases)[115]
α_{2c}-Adr. receptor (α2c-AR) - Ins/Del, AF: 0.04-0.41	Pre-synaptic inhibitory autoreceptors involved in control, release of NE from sympathetic and adrenergic neurons	↓ Agonist binding and ↓ G-protein coupling → enhanced pre-synaptic release of NE[116]	Associated w/survival in severe DCM[118]. Synergistic activity of β-blockade, improved outcome in individuals with β_1-AR Arg389Arg[111]
NE transporter (NET-182C) - T-182C, AF: 0.27-0.47	Regulate reuptake of pre-synaptic NE	Located in promoter 5' region of NET gene, alters transcription regulation[108]	T-182C associated with improved LVEF while on β-blockers 182CC resistant to β-blockade[108]
Cytochrome p450 (CYP2D6)[119] - 12 Variations, AF: 0.05-0.40	Encodes for the cytochrome p-450 (CYP) 2D6 enzyme which is involved in metabolism of beta blockers[120]	Extensive metabolizers: 2 wild-type alleles; Intermediate: one wild-type and partially deleted; Poor metabolizers (PM): 2 null alleles.	Poor metabolizers (2 null alleles) require higher dose of carvedilol to achieve therapeutic levels when compared to those who are not.[110]

Abbreviations: Adr, Adrenergic; CO, cardiac output; HR, heart rate; cAMP, cyclic AMP; NE, norepinephrine; DCM, dilated cardiomyopathy

2.6 Significance

There is convincing evidence that childhood cancer survivors treated with HD-anthracyclines are at risk of developing A-HF, and that the risk increases with duration of follow-up.[3,25,33,104,121,122] It is also well-recognized that for adult non-oncology populations, early intervention is critical for reversal of neuro-hormonal imbalance and myocardial remodeling which occurs following ischemic or non-ischemic injury.[19,20,123] In addition, among children with genetic predisposition to dilated cardiomyopathy, secondary pharmacologic intervention has been shown to significantly improve long-term cardiovascular outcomes.[60] There is a paucity of well-conducted randomized interventional trials in childhood cancer survivors at high-risk for A-HF. Previous studies have shown that while ACE-inhibition may attenuate myocardial remodeling, this improvement is short-lived.[61,62] By providing combined β1, β2, and α1 blockade, carvedilol has the potential to *reverse* early myocardial remodeling in this high risk population.[17] Given that cardiovascular complications are a leading cause of morbidity and mortality in long-term

survivors of childhood cancer, we are compelled to develop targeted intervention studies for those at highest risk. Thus, we propose a comprehensive pharmacologic intervention trial for reversal of LV myocardial remodeling in childhood cancer survivors who have received HD-anthracyclines as part of the management of their cancer.

2.7 Hypotheses

We hypothesize that carvedilol delivered at a dose of 12.5 mg per day for two years will be an efficacious and safe option for HF risk reduction in childhood cancer survivors at very high risk of developing HF due to previous exposure to high-dose anthracyclines. We also hypothesize that there exists a subgroup within the patient population who will derive the most benefit from taking carvedilol for HF prevention with least risk.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry Module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be

accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

After the initial COG registration and enrollment, all data entry will go directly to the coordinating center at City of Hope.

3.1.4 Timing

Patients must be enrolled before taking the first dose of study drug. The date that study drug is projected to start must be within 45 days of the eligibility screening.

If eligibility screening procedures were completed on multiple days, patients must start the study drug within 45 days of the first day.

Patients who are found ineligible for enrollment, and were never enrolled on ALTE1621, may be brought back at a future date for rescreening, if in the investigator's judgment, the relevant exclusion criteria no longer apply. A repeat screening visit will be scheduled at such time that the investigator believes the patient is likely to meet all study inclusion and exclusion criteria. A patient may be screened for eligibility no more than 2 times.

The required observations for the eligibility screening are listed in Section 7.1.

3.1.5 Inclusion of Women and Minorities

Both male and female subjects of all races and ethnic groups are eligible for this study.

3.1.6 Randomization

Randomization will occur after enrollment and must be completed within 45 days of the eligibility screening. If randomization and enrollment are taking place on the same day, then randomization can take place before enrollment. This will allow ample time for the pharmacist to receive the kit assignment.

If eligibility screening procedures were completed on multiple days, patients must be randomized within 45 days of the first day.

Randomization will take place through a third party drug distributor called "Sharp Clinical Services" (Phoenixville, PA). See the "Study Drug Packet" on the ALTE1621 web page on the COG website for details on timing and randomization through the IVRS system.

Sharp Clinical Services will randomize the subject to carvedilol or placebo using a blocked, stratified randomization design with age at diagnosis (2 strata: < 5 years, ≥ 5 years), time since diagnosis (2 strata: < 10 years, ≥ 10 years), and cardiac irradiation (2 strata: any, none), as stratification factors (8 strata total) and a block size of 4 to balance the number of participants in each arm. Blinded study drug will then be assigned to the patient. City of Hope, the coordinating center, will be notified that randomization is complete.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Current Weight for Males and Females

3.2.1.1 Males and Females must weigh ≥ 40 Kg.

3.2.2 Age at Cancer Diagnosis

Patient must have had a cancer diagnosis < 22 years of age, irrespective of current age.

3.2.3 Lifetime Anthracycline Dose

Patient must have a lifetime cumulative anthracycline dose of ≥ 250 mg/m^2 DOXOrubicin equivalent without the protection of dexrazoxane (Zinecard) therapy (see Section 3.3). The anthracycline dose threshold must be met as part of the treatment of a cancer that was diagnosed at < 22 years of age.

Note: Institutional records (e.g., clinic note, treatment summary, chemotherapy roadmap) can be used to document lifetime receipt of anthracycline dose.

3.2.4 Timing from Cancer Treatment to Study Entry

Patient must have completed cancer treatment ≥ 2 years prior to study enrollment.

EXCLUSION CRITERIA

3.2.5 Cardiac Treatment or Conditions

3.2.5.1 Receiving treatment for cardiomyopathy or heart failure.

3.2.5.2 Ejection fraction of < 50% (by radionuclide angiogram or echocardiogram) or shortening fraction of < 25% (by echocardiogram).

Note: for instances where both are reported, and one is below the threshold, the site will have the option to re-measure it centrally at the core lab.

3.2.5.3 Uncorrected primary obstructive or severe regurgitative valvular disease:

- Nondilated (restrictive); or
- Hypertrophic cardiomyopathy; or
- Significant systemic ventricular outflow obstruction.

3.2.5.4 Sustained or symptomatic ventricular dysrhythmias uncontrolled with drug therapy or implantable device.

3.2.5.5 Significant conduction defects (i.e. second or third degree atrio-ventricular block or sick sinus syndrome).

3.2.5.6 Bradycardia: heart rate < 50 Beats per minute (BPM).

3.2.5.7 Use of an investigational drug or beta adrenergic blockers, including metoprolol, sotalol, within 30 days of enrollment.

3.2.5.8 History of drug sensitivity or allergic reaction to alpha or beta-blockers.

3.2.6 Low Blood Pressure or Blood Pressure Medication

3.2.6.1 Low resting systolic blood pressure: < 90 mmHg.

3.2.6.2 Use of any other blood pressure lowering medication for treatment of hypertension within 30 days of enrollment except calcium channel blockers and diuretics.

3.2.7 Other Exclusion Criteria

3.2.7.1 History or current clinical evidence of moderate-to-severe obstructive pulmonary disease or reactive airway diseases (i.e. asthma) requiring therapy.

3.2.7.2 Serum AST and/or ALT > 3 times upper limit of institutional normal.

3.2.7.3 Gastrointestinal, or biliary disorders that could impair absorption, metabolism, or excretion of orally administered medications.

3.2.7.4 Endocrine disorders (such as primary aldosteronism, pheochromocytoma, hyper- or hypothyroidism) not controlled with medication.

3.2.7.5 Uncontrolled diabetes (Controlled diabetes per the American Diabetes Association and International Diabetes Center's Glycemic Target Goals is Hemoglobin A1C < 7%).

3.2.7.6 Anemia (hematocrit < 28%).

3.2.7.7 Currently using select CYP2D6 inhibitor or inducer medications (full list, see Section 6.1.7).

3.2.7.8 Inability to swallow pills.

3.2.8 Pregnancy and Breast Feeding

3.2.8.1 Female patients who are pregnant are not eligible. Women of childbearing potential require a negative pregnancy test prior to starting study drug.

3.2.8.2 Lactating females are not eligible unless they have agreed to not breastfeed their infants.

3.2.8.3 Sexually active female patients of reproductive potential are not eligible unless they agree to use an effective contraceptive method during study and for 2 months after stopping the study drug. Abstinence is an acceptable method of birth control.

3.2.9 Regulatory Requirements

3.2.9.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.9.2 All institutional, FDA, and NCI requirements for human studies must be met.

3.3 Cumulative Anthracycline Dose Calculation

Lifetime cumulative anthracycline dose will be calculated by multiplying the total dose of each anthracycline (doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone) by a factor that reflects the cardiotoxic potential of each drug and then summing the individual doses.[124] Conversion factors are shown in Table 2. Any anthracycline dose given with Dexrazoxane will not be counted towards the cumulative dose. Patients who received more than one anthracycline prior to study entry should have each individual agent cumulative dose converted to doxorubicin equivalent and added together (e.g., a patient who received

Table 2. Anthracycline Conversion

Agent	Conversion Factor to Doxorubicin Dose
Doxorubicin	Multiply total dose x 1
Daunorubicin	Multiply total dose x 1
Idarubicin	Multiply total dose x 5
Mitoxantrone	Multiply total dose x 4
Epirubicin	Multiply total dose x 0.67

cumulative dose of Daunorubicin at 200 mg/m^2 and Mitoxantrone 48 mg/m^2 has a total doxorubicin dose equivalent of 392 mg/m^2 (200 mg/m^2 x 1 + 48 mg/m^2 x 4)).

3.4 Recruitment

Each institution should follow the best recruitment strategy for their site and patients. The below recruitment procedures are recommendations only.

3.4.1 Retrospective Recruitment

Prior participants in any of the active COG long-term cancer survivorship clinics or associated clinical registries who are alive and eligible based on medical record review will be mailed a letter and study brochure describing the study. The letter lets them know that a representative from the study will be calling to tell them more about the study, unless they opt out (i.e., passive refusal). Upon contact, the patient will be given another opportunity to opt out. Patients who agree to be prescreened will be interviewed per the Phone Scripts (see study web page).

3.4.2 Prospective Recruitment

The study will be introduced to eligible patients at the end of their survivorship clinic visit; a brochure describing the study will be given to eligible subjects to take home to read. The study clinical research associate (CRA) or clinical research nurse (CRN) will then follow up with a phone call within approximately 7-10 days to assess interest and confirm interest in eligibility screening. Patients may also self-identify and call in to a local site via recruitment advertising.

3.5 Eligibility Screening

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility), and no more than 45 days before enrollment, may be used for baseline values even if the studies were done before informed consent was obtained.

3.5.1 Eligibility Screening

Patients will undergo an eligibility screening to assess all the inclusion and exclusion criteria. Patients may be screened and enrolled at the same visit; however, all screening procedures must be completed and reviewed prior to enrollment. All required observations for the eligibility screening are listed in Section 7.1.

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Subjects will be randomized 1:1 to receive low-dose carvedilol or placebo daily for 24 months. Randomization will be stratified according to rules outlined in Section 3.1.6. Subjects will be instructed to swallow the capsule whole, with water or another non-alcoholic liquid, preferably at the same time each day. They may take the capsules with food. If they forget a dose, participants will be asked to take it when they remember, and then take the next dose as usual, but if they do not remember until their next dose, do not take extra capsules to make up the missed dose.

4.2 Concomitant and Repeat Therapy

No concomitant therapy is allowed with the exception of continued medications for chronic illnesses and necessary medications for unrelated acute illnesses that may occur during the study (cold, flu, infection, etc.). Any such medications must be recorded.

4.3 Dose Escalation and Up-Titration Period

The goal of the up-titration period is to reach the highest dose level that will be continued throughout the maintenance phase. After enrollment and randomization, all subjects will be entered into the up-titration period, during which they will receive carvedilol or placebo. The first dose of the double-blind medication will be administered with food at the clinic. At one- and two- hours after administration of the dose, heart rate and blood pressure will be assessed. The first titration of carvedilol (or matched placebo) will occur two weeks following randomization (± 2 calendar days), with the subsequent titration occurring four weeks later (± 7 calendar days). The initial daily dose will be 3.125 mg once daily. The target final titration dose will be 6.25 mg twice daily (BID) (standard schedule, carvedilol dosing).

The titration dose levels of carvedilol or matched placebo are:

Level	Dose	Frequency
1	3.125 mg	once daily (QD)
2	6.25 mg	once daily (QD)
3	6.25 mg	twice daily (BID)

During the up-titration from level 1 to 2, subjects will be instructed to not take their usual dose of the study medication the morning of their study visit. This dose will be given in clinic, after visit assessments have been completed.

For titration from level 2 to 3, subjects will be instructed to take their daily carvedilol dose the evening prior to their clinic visit, and to refrain from taking the study medication the morning of their study visit. This dose will be given in clinic, after visit assessments have been completed.

At each up-titration visit, the following parameters will be assessed:

- Interim history and physical examination (except Day 0).
- Sitting pre-dose blood pressure and heart rate.
- Sitting 1- and 2-hour post-dose blood pressure and heart rate.
- Concomitant medication assessment.
- Study medication compliance using the Adherence Tracking Form (except Day 0).
- Investigator's assessment of subject's ability to tolerate the study medication, including acute tolerability for at least 2 hours after the first dose of each up-titration level.

If the dose level is judged by the investigator to be tolerated based on the criteria in Section 4.3.1, the dose of carvedilol or matching placebo will be increased to the next level.

4.3.1 Criteria for Assessment of Drug Tolerability Prior to Dose Escalation

The goal of the up-titration period is to reach the highest dose level that will be continued throughout the maintenance phase. Subjects who are unable to tolerate escalation from dose level 1 to 2 (Day 14) will go off protocol therapy. Subjects at dose level 2 will be escalated to dose level 3 or maintained at level 2, depending on tolerability. Dose tolerability will be determined following administration of study drug in clinic. Symptoms will be monitored for a minimum of 2 hours post medication administration. Individuals who meet the following criteria at the end of the evaluation period will be deemed ineligible for dose escalation:

- Low resting systolic blood pressure: < 90 mmHg.
- Bradycardia: heart rate < 50 BPM.
- Sustained or symptomatic ventricular dysrhythmia. Significant conduction defects (i.e. second or third degree atrio-ventricular block) on ECG.
- Dizziness: moderate unsteadiness or sensation of movement (Grade 2 toxicity).
- Flushing: moderate symptoms, limiting instrumental ADL (Grade 2 toxicity).
- Other reasons not listed above, but deemed related to study drug per the investigator.

Prior to escalation to the next dose level, investigators will complete a Dose Escalation Form, confirming that the individual did not demonstrate any of the above signs or symptoms.

4.3.2 Subjects on Dose Level 1 (3.125 mg/Placebo Daily)

At two weeks post-randomization, subjects will return to clinic for a clinical evaluation. During that visit, there will be two options:

- Increase to level 2, *or*
- If dose escalation is considered inadvisable by the investigator, to discontinue the study drug.

Subjects unable to tolerate dose level 1 should be taken off therapy per Section 8.0. Adverse events that occur within 30 days of study drug discontinuation must be reported and followed to resolution. Adverse events considered to be of suspected or probable or definite relationship to study medication will be reported and followed to resolution whenever they occur (see Section 8.1). The reason for removal from protocol therapy will be recorded.

4.3.3 Subjects on Dose Level 2 (6.25 mg/Placebo Daily)

Four weeks following escalation from dose level 1 to 2, subjects will return to clinic for a clinical evaluation. During that visit, there will be two options:

- Increase to dose level 3, *or*
- Maintain at the current dose level if dose escalation is considered inadvisable by the investigator.

Individuals on dose level 2 who are unable to tolerate dose escalation to level 3 have the option to return in 2 weeks, where there will be another attempt at dose escalation. If at that time, dose escalation is not considered advisable by the investigator, then subjects will remain on dose level 2 for the duration of the study. For these individuals, dose level 2 will be considered the fixed maintenance dose.

4.4 Maintenance Period

At the completion of the up-titration period, subjects will enter the maintenance phase of the study which will last 24 months from the first dose of study drug. For the purposes of this study, the initial maintenance visit will be synonymous with the "end of up-titration" visit. Subjects will enter the maintenance phase receiving the highest dose of study medication that was tolerated in the up-titration phase. This may be dose level 2 or 3.

During the maintenance period, study visits will be scheduled on 90, 180, 365, 540, and 730 days. These study visits may occur within +/- 10 business days of the calculated visit day. Additional visits may be scheduled by the investigator, as appropriate, based on clinical indication. The study CRA/CRN will follow-up with a telephone call in between clinic visits, as outlined below.

4.5 Follow-up Visits

Study participants will be asked to return their pill kits on Day 90 for a pill count, refill of the medication, and clinical evaluation; patient reported symptoms will be accessed via a standardized Symptom Log (see study web page on the COG website). For the Day 90 visit only, the patient has the option to do an in-person visit or a phone follow up, depending on their ability to easily return to the clinic.

Subsequent return clinic visits will occur on Days 180, 365, 540 and 730 following randomization. The following parameters will be assessed according to the study observations (see Section 7.1).

On Days 270, 455, and 630 a phone visit will be conducted (these calls may occur within ± 10 business days of the calculated due date). During the telephone call, there will be collection of patient reported symptoms via standardized Symptom Log, medication refill, and pill count reported on the Adherence Tracking Form.

A City of Hope Adverse Event (AE) collection form will be submitted by study personnel on Days 180, 365, 540, and 730.

4.6 Long-term Follow-up

After trial completion, study participants will continue clinic follow-up per standard of care, with their first return visit scheduled one year after their Day 730 study visit. All organ function assessments included in the COG survivorship guidelines

(www.survivorshipguidelines.org) should be performed, including an echocardiogram. Special attention should be paid to symptoms and signs of cardiac dysfunction on all subsequent annual follow-up survivorship clinic visits. Follow up should be reported using the long-term cardiac outcomes report form for 3 years after the Day 730 study visit.

Monitoring for cardiac dysfunction that may occur after the two-year intervention, will occur during the annual survivorship clinic visits which will include a complete physical examination and an echocardiogram per the COG survivorship guidelines. Information regarding new cardiac events will be obtained from the survivorship clinic using the Cardiac and Other Event Form.

5.0 EMERGENCY UNBLINDING

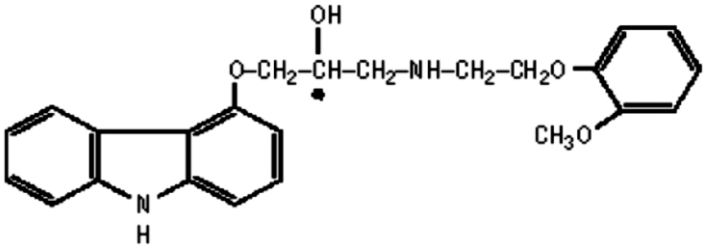
Only in the event of a serious adverse event wherein the investigator feels that the patient cannot be adequately treated without knowing the identity of the study medication may the medication code be broken for a particular subject. If emergency un-blinding is required, [redacted] must be contacted as soon as possible. The Study Chair or Vice-Chair will log onto the Sharp Clinical Services website, unblind the patient, and contact the site investigator with the drug or placebo information. In the event of un-blinding, the patient will be removed from protocol therapy.

6.0 DRUG INFORMATION

6.1 Carvedilol (IND exempt, Coreg®, NSC #751177) (06/28/17)

6.1.1 Source and Pharmacology:

Carvedilol is a racemic mixture in which nonselective β-adrenergic blocking activity is present in the S(-) enantiomer and with α1-blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity. It is (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. Carvedilol is a racemic mixture with the following structure:



Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of C24H26N2O4. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, pH 1.1), and intestinal fluid (simulated, without pancreatin, pH 7.5).

Pharmacokinetics: Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the

apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability.

Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade.

Compared to carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent. Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes are CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-mephenytoin (patients deficient in cytochrome P450 2C19).

Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min.

Pregnancy: There are no adequate and well-controlled studies in pregnant women.

6.1.2 Toxicity

Incidence	Toxicities
Common (>20% of patients)	• **Fatigue** • **Dizziness**
Occasional (4-20% of patients)	• **Hypotension** • **Pain in chest** • **Bradycardia** • **Shortness of breath** • **Generalized edema** • **Peripheral edema** • **Syncope** • **Headache** • **Nausea** • **Diarrhea** • **Weight gain** • **Hyperglycemia** • **Dry mouth** • **Insomnia** • **Blurred vision** • **Anxiety** • **Concentration impairment**
Rare (<3% of patients)	• **Paresthesia** • **Muscle cramps** • **Blurred vision** • **Impotence** • **Insomnia** • **Anemia** • **Thrombocytopenia** • **Hypersensitivity reaction** • **Stevens-Johnson syndrome or toxic epidermal necrolysis**
Pregnancy & Lactation	**Females of childbearing age should avoid pregnancy while taking study medication and for two months after discontinuation. The use of barrier or other contraceptive measures is strongly recommended during the study period and for two months thereafter.** **It is not known if carvedilol is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.**

6.1.3 Formulation and Stability:

Carvedilol 3.125 mg, 6.25 mg capsules, and matching placebo will be shipped at room temperature. The capsules should be stored at a controlled room temperature of 20-25°C (68-77°F) in the 3-month supply kits. Temperature excursions up to

30°C are allowed without concern for stability of the drug. Carvedilol or matching placebo will be stored and dispensed in the original containers.

6.1.4 Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol, Section 4.0.

6.1.5 Supplier:
Carvedilol is available in 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg tablets. For this trial, generic 3.125 mg and 6.25 mg capsules and matching placebo capsules will be manufactured by Sharp Clinical Services (Phoenixville, PA). **Do not use commercial supply.**

6.1.6 Obtaining the Agent:
Agent Ordering:
Distribution of study drug will be performed by a third party at Sharp Clinical Services. Details regarding drug randomization and distribution are on the study web page (see "Study Drug Packet").

Agent Returns:
All unused or expired study drug should be destroyed per institutional guidelines.

6.1.7 Drug Interactions:
The following drugs have been reported as inhibitors or inducers of CYP2D6 which is the major P450 enzyme that metabolizes carvedilol. Concomitant use of strong and clinically significant moderate inhibitors will not be allowed while on study.

Strong CYP2D6 inhibitors ***(not allowed on study):***	desvenlafaxine
bupropion	diphenhydramine *
fluoxetine	doxepin
paroxetine	doxorubicin
quinidine	escitalopram
Clinically significant	halofantrine
moderate CYP2D6 inhibitor	haloperidol
(not allowed on study):	hydroxyzine *
duloxetine	labetolol
Other moderate CYP2D6 inhibitors	levomepromazine
(should be avoided while on study):	lopinavir
cinacalcet	methadone
mirabegron	metoclopramide
terbinafine	midodrine
Weak CYP2D6 inhibitors	moclobemide
(should be avoided while on study):	perphenazine
amiodarone	ranitidine *
cimetidine	ritonavir
thioridazine	ticlopidine
Other possible CYP2D6 inhibitors	tipranavir
(will be tracked on study):	tripelennamine
celecoxib	sertraline
chlorpheniramine*	vemurafenib
chlorpromazine	other histamine H1 receptor
citalopram	antagonists**
clemastine *	***Possible CYP2D6 inducers***
clomipramine	***(will be tracked while on study):***
	dexamethasone
	rifampin
	Virtually no effect on CYP2D6:
	venlafaxine (Effexor) – *preferred antidepressant while on study*

*Available over the counter
**Examples: cetirizine, dimenhydrinate, doxylamine, fexofenadine, loratidine, meclizine, pheniramine

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required Clinical, Laboratory and Disease Evaluations

Studies	PRIOR to Enrollment	Days on Study Drug										
	Eligibility Screening	1st day of drug	14 ±2 calendar days	42 ±7 calendar days	90@	180	270	365	455	540	630	730
					±10 Business Days							
History and physical	X		X	X	X@	X		X		X		X
Cardiac Evaluations												
Echocardiogram&	X					X		X		X		X
Electrocardiogram	X		X	X								
Lab Tests												
Pregnancy Test*	X											
Hematocrit Blood Draw	X											
Biomarkers Blood Draws (see Section 10.3)	X					X		X		X		X
CBC and Comprehensive Metabolic Panel (Creatinine, liver panel (bilirubin, AST/ALT))	X					X		X		X		X
Questionnaires (available in English and Spanish)												
Demographics, Medical and Family History Forms	X											
HRQoL Form	X					X		X		X		X
Treatment Management and Adherence Monitoring												
Follow-up phone call#					X@		X		X		X	
Symptom Log, Study Tablet dispersal		X	X	X	X	X	X	X	X	X	X	X%

& COG institutions will receive additional per-case reimbursement for this study to allow institutions to pay for the two echocardiograms (month 6 and month 18) that are not considered standard of care.

@ For the Day 90 visit only, the patient has the option to do an in-person visit or a phone follow up, depending on their ability to easily return to the clinic. If Day 90 is a phone follow up, the History and Physical is not required.

* Women of childbearing potential require a negative pregnancy test prior to starting study drug; females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during the study and for at least 2 months after the last dose of study drug. Abstinence is an acceptable method of birth control. For female participants of childbearing age, investigators will follow-up regarding their pregnancy status at each clinic visit. A pregnancy test is required at the eligibility screening and then throughout the study period as deemed necessary by the investigator.

Follow-up phone calls are to confirm medication tolerance after the screening day and in-between clinic visits to determine (and reinforce) adherence, complete the Symptom Log, and arrange medication refill. The medication refills are either picked up by the patient or sent via FedEx to their home.

% No study medication is dispensed at Day 730.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Physician determines it is in the patient's best interest.
b) Inability to tolerate dose escalation from level 1 to level 2.
c) Treatment interruption longer than 90 consecutive days.
d) A cardiac event (see Section 8.1.1 for definition).
e) Pregnancy.
f) Adverse Event requiring removal from protocol therapy (see Section 13.4).
g) Diagnosis of a new malignancy requiring systemic chemotherapy or radiation.
h) Adherence < 50% in any 90 day period.
i) Emergency un-blinding (see Section 5.0)
j) Study is terminated by Sponsor.

Patients who are taken off protocol therapy do not require any additional study observations/evaluations unless they experienced a cardiac event or have become pregnant.

8.1.1 Study End Form

All patients withdrawn from study medication must have the reason for withdrawal recorded on the Study End Form located on the ALTE1621 webpage on the COG website (including subjects who complete the study). All adverse events leading up to withdrawal of study medication must be fully documented and followed up as appropriate. To ensure that all withdrawals due to adverse events are correctly identified, "Adverse Event" should only be marked as the reason for withdrawal on the Study End Form for those patients whom an adverse event was considered to have been the direct cause of withdrawal from the study medication. This is particularly important when adverse events are ongoing at the time of withdrawal, but the reason for withdrawal is not related to the adverse event.

A cardiac event is defined as: 1) acute heart failure with pulmonary edema and S3 gallop without obvious correctable cause (i.e., intravenous fluid overload during surgery), or 2) EF < 50%, shortening fractional (SF) < 25% or a 20% drop from an earlier test. Subjects who develop a cardiac event while on study will be referred to a cardiologist for proper diagnostic work-up and management. These individuals will be taken off study drug.

Participants must not be planning to become pregnant for two years to be eligible for the study, and they will be warned about the importance of not becoming pregnant while on study at the time of enrollment. They will be advised to use contraception for all sexual activity during the course of the study and for 2 months afterwards. Nevertheless, occurrence of an unplanned intrauterine pregnancy while on study will be an indication for immediately stopping treatment and the patient must withdraw from the study. If the patient should become pregnant while on study, or within 2 months after discontinuing therapy, her treatment assignment will be unblinded immediately (see Section 5.0). Whenever possible, a pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to the study team after delivery.

8.2 Off Study Criteria

a) Withdrawal of consent for any further data submission.
b) Death.
c) Completion of planned study assessments.
d) Lost to follow up (defined as no contact with patient for ≥ 90 consecutive days after a required observation).

9.0 STATISTICAL CONSIDERATIONS

The following section includes the protocol that was active at the time of study initiation and amendments that were made resulting from a reduction in study sample size from 125 per arm to **91** per arm. With Amendment #4, revisions were made to the detectable treatment effect size and interim analyses. The analysis plan remains the same.

9.1 Study Design

This is a Phase 2b randomized double-blind placebo controlled clinical trial to examine the effect of carvedilol on preventing cardiovascular morbidity/mortality associated with anthracycline exposure during childhood cancer treatment. Childhood cancer survivors who were previously treated with ≥ 250 mg/m^2 cumulative dose of anthracyclines will be randomized 1:1 between the 2 arms: carvedilol arm and the placebo arm. Randomization will be stratified by age at diagnosis (2 strata: < 5 years, ≥ 5 years), time since diagnosis (2 strata: < 10 years, ≥10 years), and cardiac irradiation (2 strata: any, none), as stratification factors (8 strata total) and a block size of 4. Daily treatment with carvedilol and placebo will continue for 2 years. Cardiovascular functions will be assessed at baseline and semi-annually. The primary endpoint is LV thickness-dimension ratio (LV T-D) derived from echocardiogram.

9.2 Patient Accrual and Expected Duration of the Trial

It is estimated that approximately 50-60% of the 450,000 survivors of childhood cancer who are alive in the U.S. today have received anthracyclines. Many pediatric cancer patients (approximately 20-25%) are being treated with anthracyclines with cumulative dose ≥ 250 mg/m^2, such as those with bone cancer and AML. Although exact estimates are not available, using the conservative estimates of 50% and 20% to calculate, >30,000 survivors would meet the current eligibility criteria. We expect thousands of childhood cancer survivors meeting such criteria are currently being followed at member COG institutions.

ACTIVATION PROTOCOL:

To answer the scientific questions, 250 randomized subjects (125 per arm) is required. Through a different mechanism, 82 patients have already been accrued and randomized. Therefore, this COG protocol aims to enroll and randomize an additional of 168 patients through this protocol, with a maximum accrual of 177 patients to account for up to 5% of ineligible enrollments. Given the large pool of potential eligible patients, we expect to complete the accrual, including the time it takes to open the study at COG institutions, over 4 years.

WITH AMENDMENT #4:

To answer the scientific questions, **182** subjects (**91** per arm) who are randomized and start study drug are required. Through a different mechanism, 87 patients have already been accrued and randomized. Therefore, this COG protocol aims to enroll, randomize and start

treatment for an additional **95** patients through this protocol. To account for attrition, enrollment through this COG trial may proceed up to 109 patients. Given the large pool of potential eligible patients, we expect to complete the accrual, including the time it takes to open the study at COG institutions, over 5 years.

9.3 Data Analytic Plan

Aim 1.1: To determine the impact of a two-year course of low-dose carvedilol on surrogate echocardiographic indices of heart failure (HF) risk.

9.3.1 LV Thickness-Dimension Ratio (LV T-D)

The primary endpoint of this trial is LV thickness-dimension ratio (LV T-D) z-score. LV thickness is reported in terms of LV posterior wall dimension in systole, while LV dimension will be based on the internal diameter in diastole. Z-scores will be calculated using the formula: (LVPWD/ LVEDD – 0.18) / 0.025.[21]

LV T-D Z-score will be determined at baseline, 6 months, 12 months, 18 months and 24 months. The z-scores will be appropriately transformed to normality as necessary. The analysis will be conducted accounting for correlation among repeated measurements within individuals. This may be done using the Generalized Estimating Equation (GEE) approach or by the restricted maximum likelihood estimation (REML) approach with the mixed effect model with random effects. Various covariance structures will be assumed, including the unstructured, compound symmetry, and autoregressive lag-1 correlation. GEE and REML will be implemented using GENMOD and MIXED procedures in SAS.

LV T-D z-scores will be modeled as a linear function of time. Under the intention-to-treat principle, the efficacy of carvedilol will be examined by comparing the slopes of the longitudinal linear models of LV T-D z-score between carvedilol and placebo control group. The difference in slopes by treatment group will be introduced by including an interaction term of time with group indicator (0 for placebo, 1 for carvedilol). Treatment effect will be tested by a 1-df test for the interaction. Non-linear effects will be tested by including an interaction of a quadratic term in time with the group indicator.

To examine other than the linear model, we will also fit an unstructured mean model, which is a non-parameterized model with four indicator variables of time. Interactions of the time and group indicators will be included to allow for treatment differences at follow-up time points. This will enable us to examine other than linear or quadratic trends in time.

Because of randomization, we expect no difference between the expected values of LV T-D z-scores at t0 between the treatment groups. However, we will evaluate the success of the randomization by examining between-group differences in demographic and clinical characteristics (i.e. age at anthracycline exposure, chest radiation, time from treatment), study site, as well as the mean LV T and D z-scores at baseline. If imbalance is evident, our analysis will take into account the covariates with significant imbalance.

Low dose carvedilol will be considered effective if the 1-df test in the linear model is significant and the expected LV T-D z-score is lower for placebo at follow-up

time points, indicating the effectiveness of low-dose carvedilol in preserving LV T-D.

In addition to unadjusted analyses which are appropriate under the randomization principle, adjusted analysis will also be performed. Significantly imbalanced covariates and covariates known to be prognostic for HF, such as age at anthracycline exposure, chest irradiation, and time from completion of treatment, will be incorporated in the longitudinal models before including and testing the time by treatment group interaction.

To address potential noncompliance, we will also conduct an as-treated analysis, considering patients' actual treatment uptake. Instead of the treatment indicator (placebo or carvedilol), we will include adherence rate, i.e. 0 for placebo and a number between 0 and 1 for carvedilol determined by pill count, in the linear mixed effects model. Time-specific adherence rate and the overall adherence rate will be considered. If carvedilol is effective, we may expect to see an increase in LV T-D z-score and a greater difference in slope with increasing adherence rate.

The estimates from linear mixed effects model are valid in the presence of incomplete response data if missing data occurs at random. However, nonparticipation and dropouts may occur differentially between treatment groups for various reasons, possibly resulting in non-ignorable missing data. In addition to collecting information on reasons for nonparticipation, we will apply two analytic approaches to examine the effects of missing data on study results:[125] 1) pattern mixture models and 2) selection models. In pattern mixture models, the 16 possible missing data patterns (arising from 4 follow-up time points, with no missing data at t0, and considering a response as missing if data from echocardiographic assessment are missing) will be used as covariates in the above-described bivariate linear mixed effects model. The effects of missing data on the estimate of treatment effect can be assessed. An overall estimate of the treatment effect may be obtained by averaging the estimates over the missing pattern groups. In the selection model, we will model the probability of dropout using baseline covariates to estimate the propensity for dropout. The propensity scores will be used as a covariate in the bivariate linear mixed effects model to adjust for the effects of dropout on treatment effects.

Secondary echocardiographic efficacy measures (afterload, systolic and diastolic measurements) will be evaluated by applying the same methods for longitudinal analysis. Significance of the carvedilol effects will be evaluated in the manner described above based on testing the significance of the interaction of time by group indicator variables. The distribution of continuous variables will be examined graphically and appropriate transformations made before applying analytical methods based on normal assumption.

9.3.2 Blood Biomarkers of Myocardial Remodeling

Natriuretic peptides (BNP), cardiac troponins (cTnT and cTnI), and Galectin-3 will be treated as continuous measures. We will apply the linear mixed effects model for between group comparisons of measures from the 5 time points. The unstructured mean model and linear in time model will be employed.

Aim 1.2.1: To establish the safety and tolerability of low-dose carvedilol.

9.3.3 Objective Safety Measures

Adverse events. The number of Grade 2-4 toxicities observed will be tabulated by treatment arm. Differences by treatment arm will be evaluated using Fisher exact tests.

Biomarkers. Liver function measurements (Bilirubin, AST, ALT) will be treated as continuous variables. Study participants will be considered to have elevated liver function if the measurements at 6, 12, 18, and 24 months are above the upper limit of the institutional reference range and higher than baseline pre-treatment level. These data will be coded such that those who are greater than 2-times the upper limit of the reference range will be considered to be clinically significant (Grade 1 if asymptomatic and requiring no intervention; Grade 2 if minimal/local/non-invasive intervention required). The frequency of individuals with elevated liver function measures will be compared between treatment groups using an exact test on 2x2 tables, stratified on CYP2D6. Logistic regression analysis will also be used to compare the frequency of elevated liver function between treatments, adjusted for covariates. Linear mixed-effects model for normally distributed data will also be used to compare the trends in liver function levels between the treatment groups. Procs MIXED and GLIMMIX will be used for longitudinal analysis of normally and non-normally distributed data, respectively. Proc GENMOD will also be used for normally and non-normally distributed data.

9.3.4 Subjective Safety and Tolerability Measures

Treatment adherence. Patients will self-report adherence in the study questionnaires. Compliance will also be measured by pill counts performed every 3 months. The number of pills taken out of the total prescribed in a 3- month period will be modeled as a random effects binomial regression model.[126] The binomial rates from 8 time points (month 3 to 24) will be modeled as unstructured mean model with 7 indicator variables as well as polynomial models over time. The random-intercept and the random intercept and slope models will be considered. The significance of the time indicators or parameters by treatment interaction will be evaluated for treatment difference in compliance.

Voluntary withdrawals will be examined at the end of the study by comparing the percent of withdrawals between the treatment groups using a chi-square test or Fisher's exact test.

Patient reported symptoms. The outcomes will be scored as a 5-point Likert-type scale (0 to 4) in response to questions on how much the patients are bothered by certain symptoms. The questionnaire will be administered at Days 0, 14, 42 and 90, and every three months after Day 90, for a total of eleven time points. The responses will be treated as normally distributed, as ordinal or dichotomized variable, and we will apply the linear mixed effects model or generalized linear mixed effects model methods to compare changes between treatment groups. Because of additional time points available, in addition to the unstructured mean model, we will also fit piecewise models with join point at 6 months, considering linear and curvilinear trajectories between 6 m and 24 m time points.

Aim 1.2.2: To examine the modifying effects of demographic, clinical, and molecular characteristics on both efficacy and safety markers.

As the primary aim of this trial is to examine the main effects of low-dose carvedilol on LV-TD z-score, we will examine the modifying effects of demographic, clinical, and molecular characteristics as exploratory analysis. Even if time by treatment interaction (main treatment effect) is not significant, examining the modifying effects of covariates may reveal subgroups that respond differently to carvedilol. A three-way interaction of time by treatment by modifying variable will be included in the longitudinal model containing a two-way time by treatment group interaction. Modifying effects will be considered statistically significant if the three-way interaction is significant. The covariates of interest are described below.

A. Patient demographics

The following variables are known to affect HF risk and LV T-D.

Attained age – continuous, time-varying variable.

Body mass index (BMI) – continuous, time-varying variable. It will also be grouped into ordinal categories: underweight (<19), normal weight (19-24), overweight (25-29), obese (30-39), morbidly obese (40+).

Cardiovascular disease – coronary artery disease (angina, acute myocardial infarction, coronary artery bypass graft surgery [CABG], percutaneous coronary intervention), ventricular or atrial arrhythmias, cerebrovascular disease, congenital heart lesions.

CV risk factors – Hypertension, dyslipidemia, diabetes, renal insufficiency, chronic lung disease, thyroid disorder, smoking history (includes smoking status, and if quit, date of cessation). All CV risk factors will be recorded as dichotomous variables (present/absent), with recording of date of onset.

Family history of cardiovascular disease – dichotomous (yes/no), constant over the study period. Outcomes of interest will include: sudden cardiac death, conduction system disease, cardiomyopathy, and coronary artery disease (CAD). For the CAD, we will also examine the frequency of the following classifications: 0 = no direct blood relatives (parents, siblings) with CAD; 1 = one or more with CAD at age ≥ 55 years for male relatives or ≥ 65 years for female relatives; 2= one or more with CAD at age less than 55 years for male relatives or less than 65 years for female relatives.

B. Clinical treatment characteristics.

The following variables are known to influence HF risk among childhood cancer survivors.

Chest radiation – continuous, time-invariant. We will also dichotomize per the stratification factor for randomization.

Age at exposure to anthracyclines – continuous, time-invariant. We will also categorize per the stratification factor for randomization.

Latency from radiation therapy – continuous, time-varying. We will examine if intervention effects vary by time since exposure to therapeutic radiation.

C. Molecular characteristics

The following variables are known to influence efficacy of carvedilol in the treatment of HF patients and will be analyzed at a later date.

CYP variants – dichotomous (yes/no), constant over the study period

$\beta_{1,2}$ and α_1-Adrenergic receptor and Norepinephrine transporter variants (Section 2.5) – dichotomous (yes/no), constant over the study period.

In addition to testing their significance as effect modifiers, we will also examine their relationship with the outcome variables (LV T-D, ESWS, Natriuretic peptides, MPI etc.) to validate known relationships. Proc Mixed for normal data and Proc GLMMIX for non-normal data in SAS 9.1 (Cary, North Carolina) will be used for analysis.

9.3.5 Exploratory Aim 1.3:

To evaluate the long-term efficacy of carvedilol in preventing cardiomyopathy and/or heart failure in high-risk childhood cancer survivors.

For this exploratory aim, long term overall and cardiac health status will be described for study participants and as exploratory analyses compared between the 2 study arms.. The majority of these childhood cancer survivors are expected to be in active follow-up and routine clinical information (including annual echocardiograms) is already being collected as part of the patients' standard care. In support of this aim, ascertainment of basic information regarding overall and cardiac health status: vital status, development of cardiomyopathy/heart failure, most recent ejection fraction and shortening fraction data in order to determine if there has been a cardiac event (as defined in Section 8.1.1) for up to 5 years after study enrollment.

9.4 Power and Sample Size

Primary Aim - Determine the impact of a two-year course of carvedilol on LV T-D: For sample size calculation, we let Y, the response, be the z-score expected for LV T-D in both groups. Because of randomization, we expect no difference between the expected values of Y at t0 between treatments. However, if the intervention is efficacious, we expect the linear slopes of the two groups to diverge over time, with no significant change in the slope of LV T-D for the carvedilol arm. Power/sample size calculation was conducted by assuming a linear change in LV T-D z-score over time. With this assumption, longitudinal power calculation requires specification of the following: 1) expected values of Y at t0 the carvedilol and control arms, 2) the expected difference in Y at 24 months between the two arms, and 3) the correlations between the repeated measurements over time. These were obtained from the following sources: **1) Expected baseline value of LV T-D** was derived from a cross-sectional study evaluating cardiac function in 150 long-term survivors of childhood cancer treated with anthracyclines at City of Hope (median age at evaluation, 24.2 years, time since diagnosis 12.5 years).[127] Mean LV T-D z-score for survivors exposed to HD-anthracycline (≥ 250 mg/m^2) was -0.72 (SD 1.0), compared to -0.03 (SD 1.1) in those treated with lower doses (< 250 mg/m^2); $p < 0.05$.[127] **2) Projected decline in LV T-**

D between baseline and 24 months was derived from two clinical trials[21,128] These studies were selected because they provided reliable longitudinal data of cardiac function, obtained from multi-institutional clinical trials that used a centralized core echo lab. Patients treated with higher dose anthracyclines had a decline in LV T-D Z-score of approximately 0.2/year, providing us with an estimated rate of LV-TD decline for the placebo arm of the current study. Given these findings, we project that mean LV T-D z-score will be -0.7 at baseline for both arms of the trial, mean LV T-D z-score for the placebo arm will decline to -1.1 at the end of the 2-year intervention, and there will be preservation of LV T-D z-score for the carvedilol arm, resulting in a projected difference at 24 months between the two arms of 0.4. We acknowledge the possibility that instead of preservation of LV T-D, there could be further decline in LV T-D for the carvedilol arm, decreasing the observed effect size at 24 months to < 0.4.

ACTIVATION PROTOCOL:

Table 3. Detectable differences in endpoints by correlation estimates
Sample size: 125/arm; Attrition: 15%/yr; Power: 0.8; Type I error: 0.05

Endpoint	Baseline Value	Estimated SD	Correl. Between measurements 0.6	0.7	0.8
Primary					
LV T-D (Z)	-0.7	1.0	0.32	0.28	0.23
Secondary					
LVEDV (mL)	105.7	26.9	8.6	7.5	6.2
LVESV (mL)	45.0	11.7	3.7	3.3	2.7
LVEF (%)	60.0	5.0	1.6	1.4	1.2

However, as discussed below, the current trial will have adequate power to detect prevention effects that are 12.5% to 37.5% lower than the projected differences between carvedilol and placebo arms. **3) Correlation between measurements over time** was based on preliminary data examining LV T-D values for the 40 patients enrolled onto the clinical trial not through this COG study but through a different mechanism with at least a baseline and six month time point; the correlation between these two time points was 0.7. Since we do not know what the correlation will be after 2 years, Table 3 depicts detectable differences for correlations ranging from 0.6 to 0.8. In addition, we show detectable differences for important secondary endpoints such as: EF, LVEDV, LVESV. Of note, as in LV T-D, estimated baseline mean values for these echocardiographic endpoints and their standard deviations were derived from our recently completed study evaluating cardiac function in comparable survivors of childhood cancer,[127] as well as from patients currently enrolled on the clinical trial. Correlation between measurements over time (baseline to 6 months) for these indices ranged from 0.6 (EF) to 0.8 (LVEDV, LVESV).

The longitudinal power calculations were conducted using the program RMASS2.[129] We assumed a Type I error of 0.05, power of 0.80, 2-sided test, linear trend, and compound symmetry correlation matrix ([ρ] ranging from 0.6 to 0.8). An attrition rate of 15% per arm/year (voluntary withdrawal, discontinuation due to drug intolerance, unexpected events [pregnancy/ relapse]) was assumed, taking into consideration the observed attrition rate (13%/year) in the study to date. Table 3 shows the minimum effect size at 24 months that can be detected for a given correlation between measures. For example, with 125 individuals in each group, we have 80% power to detect a difference of at least 0.32 in LV T-D z-score between the two arms if the correlation between baseline and the 2 year LV T-D z-score is 0.6. Thus, if the absolute difference between the carvedilol and placebo arms is smaller than 0.4, the current sample size will still be sufficiently powered to detect a lower degree of remodeling prevention. With regards to the secondary endpoints of efficacy, 3-6 mL increases in LVESV, 6-10 mL increases in LVEDV, or 3-5% drops in LV

EF (from normal resting LV EF) have been associated with adverse cardiovascular outcomes in clinical trials with patients with preserved or mildly depressed EF.[130-132] Thus, effect sizes presented in Table 3 are plausible and clinically meaningful.

WITH AMENDMENT #4:

As discussed below, the current trial will have adequate power to detect prevention effects that are 8.5% to 52.5% lower than the projected differences between carvedilol and placebo arms. **3) Correlation between measurements over time** was based on preliminary data examining LV T-D values for the 40 patients enrolled onto the clinical trial not through this COG study but through a different mechanism with at least a baseline and six month time point; the correlation between these two time points was 0.7. Since we do not know what the correlation will be after 2 years, Table 4 depicts detectable differences for correlations ranging from 0.6 to 0.9. In addition, we show detectable differences for important secondary endpoints such as: EF, LVEDV, LVESV. Of note, as in LV T-D, estimated baseline mean values for these echocardiographic endpoints and their standard deviations were derived from our recently completed study evaluating cardiac function in comparable survivors of childhood cancer,[127] as well as from patients currently enrolled on the clinical trial. Correlation between measurements over time (baseline to 6 months) for these indices ranged from 0.6 (EF) to 0.9 (LVEDV, LVESV).

Table 4. Detectable differences in endpoints by correlation estimates

Sample size: 91/arm; Attrition: 19%/yr; Power: 0.8; Type I error: 0.05

Endpoint	Baseline Value	Estimated SD	Correl. Between measurements 0.6	0.7	0.8	0.9
Primary						
LV T-D (Z)	-0.7	1	0.38	0.34	0.28	0.21
Secondary						
LVEDV (ml)	105.7	26.9	10.2	9.1	7.5	5.6
LVESV (ml)	45	11.7	4.4	4	3.3	2.5
LVEF (%)	60	5	1.9	1.7	1.4	1.1

The longitudinal power calculations were conducted using the program RMASS2.[129] We assumed a Type I error of 0.05, power of 0.80, 2-sided test, linear trend, and compound symmetry correlation matrix ([ρ] ranging from 0.6 to 0.9). An attrition rate of 19% per arm/year (voluntary withdrawal, discontinuation due to drug intolerance, unexpected events [pregnancy/ relapse]) was assumed. Table 4 shows the minimum effect size at 24 months that can be detected for a given correlation between measures. For example, with 91 individuals in each group, we have 80% power to detect a difference of at least 0.38 in LV T-D z-score between the two arms if the correlation between baseline and the 2 year LV T-D z-score is 0.6. With regards to the secondary endpoints of efficacy, 3-6 mL increases in LVESV, 6-10 mL increases in LVEDV, or 3-5% drops in LV EF (from normal resting LV EF) have been associated with adverse cardiovascular outcomes in clinical trials with patients with preserved or mildly depressed EF.[130-132] Thus, effect sizes presented in Table 4 are plausible and clinically meaningful.

Secondary Aim – Establish safety and tolerability of the two-year course of carvedilol.

ACTIVATION PROTOCOL:

Adverse events: We assume the rate of Grade 2-4 toxicities in the placebo group to be low, at 5%. At the end of the study, assuming 88 individuals remaining in each arm (15% attrition/year from the original 125/ arm), the study will have at least 80% power to detect

an adverse event rate of 19.2% in the carvedilol group based on Fisher's exact test and Type I error=0.05.

Adherence to therapy: We will examine the difference in adherence rates by comparing the percent adherence by treatment group. With 125 study participants at baseline per arm, assuming a constant adherence rate of 90% in the placebo group, a between-measurement correlation of 0.6, 15% yearly attrition, and 2-sided alternative, there will be 80% power to detect an adherence rate of 75% in the carvedilol group.

Voluntary withdrawals: We assume that the proportion of patients in the placebo arm who will withdraw voluntarily by 24 months is 20% (10%/year); of note, this is less than the assumed overall attrition rate of 15%/year because attrition could occur due to other reasons such as toxicities, cancer recurrence, etc. With 125 patients in each arm at baseline, using Type I error=0.05, the study will have 80% power to detect a >15% absolute difference in the voluntary withdrawal rates between the two study arms.

WITH AMENDMENT #4:

Adverse events: We assume the rate of Grade 2-4 toxicities in the placebo group to be low, at 5%. At the end of the study, assuming 56 individuals remaining in each arm (19% attrition/year from the 91/arm at baseline), the study will have at least 80% power to detect an adverse event rate of 24.7% in the carvedilol group based on Fisher's exact test and Type I error=0.05.

Adherence to therapy: We will examine the difference in adherence rates by comparing the percent adherence by treatment group. With 91 study participants at baseline per arm, assuming a constant adherence rate of 90% in the placebo group, a between-measurement correlation of 0.6, 19% yearly attrition, and 2-sided alternative, there will be 80% power to detect an adherence rate of ≤70% in the carvedilol group.

Voluntary withdrawals: We assume that the proportion of patients in the placebo arm who will withdraw voluntarily by 24 months is 26% (13%/year); of note, this is less than the assumed overall attrition rate of 19%/year because attrition could occur due to other reasons such as toxicities, cancer recurrence, etc. With 91 patients in each arm at baseline, using Type I error=0.05, the study will have 80% power to detect a >21% absolute difference in the voluntary withdrawal rates between the two study arms.

9.5 Interim Monitoring

9.5.1 Toxicity Criteria for Study Stopping

If, on either arm, two or more cases of the same Grade 3-4 toxicity with *probably or definitely* attributions that do not resolve in 72 hours are reported in separate patients, accrual will be held until further review by the DSMC to determine whether or not the study should be stopped based on the unblinded data available at that time.

9.5.2 Plans for Interim Monitoring for Superiority and Futility

ACTIVATION PROTOCOL:

The statistician will perform up to two blinded interim analyses for efficacy and futility after 33% and 66% of patients have completed all the study endpoints. Patients that were taken off study due to an adverse event or cardiac event after

Day 180 would also be included in the interim analyses. The DSMC will stop the trial for clear evidence of superiority or futility if the test statistic on blinded data falls within the specified early stopping boundary (Appendix II, Tables s1 and s2). In both the interim and final analysis, the intent-to-treat data set will be the primary analysis group, with consideration of missing data.

WITH AMENDMENT #4:

With the amended total n=182, 114 patients are anticipated to complete all study time points, after accounting for attrition. As of 6/30/2020, 87 patients had data at all time points, corresponding to 76% of the anticipated revised sample size of n=114. Since this is close to the final expected updated sample size, no interim analysis for efficacy will be performed, but one futility analysis will be performed using the data available at 6/30/2020 (Appendix II, Table s3).

9.6 Gender and Minority Accrual Estimates

WITH AMENDMENT #4:

As detailed above in Section 9.2, the study targets to accrue and randomize 182 subjects; however, considering the 87 patients already enrolled through a separate mechanism, only 95 patients are needed to accrue through this COG protocol. To account for attrition, enrollment through this COG trial may proceed up to 109 patients.

DOMESTIC PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native					
Asian	2	3			5
Native Hawaiian or Other Pacific Islander	1	2			3
Black or African American	2	2			4
White	30	37	8	11	86
More Than One Race					
Total	35	44	8	11	98

INTERNATIONAL (INCLUDING CANADA) PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native					
Asian		1			1
Native Hawaiian or Other Pacific Islander					
Black or African American		1			1
White	3	4	1	1	9
More Than One Race					
Total	3	6	1	1	11

This distribution was derived from the R01 application, adjusted for Children's Oncology Group projections.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Parameters to be Measured

10.1.1. Parameters to be Measured PRIOR to Enrollment

There is an eligibility screening to see if the patient meets the inclusion/exclusion criteria and then the patient will be enrolled and randomized. It is possible to have all three happen at the same visit, but they would need to occur in that order (eligibility screening, enrollment then randomization). At the eligibility screening visit, a history and physical, CBC, and comprehensive chemistry panel will be performed. An echocardiogram will also be performed at that time. Additional blood will be collected and placed on hold during the screening visit to measure circulating biomarkers and for genotyping at a later date after study enrollment.

10.1.2 Specifications by Methods of Measurements

The same method and laboratory will be used to characterize each identified and reported biological endpoint at baseline and during follow-up.

10.1.3 Parameters to be Measured during Treatment

All evaluations will be measured per the study calendar schedule using the echocardiography and assay methodology outlined in Section 10.2. Analysis of results is fully described in Section 9.3.

The following are biologic response endpoints:

1. Echocardiographic indices of myocardial remodeling and HF risk: LV T-D, ESWS, MPI, LVEDD, IVRT, E/A ratio, LVESD, WMSI.
2. Blood biomarkers of myocardial remodeling and HF risk: Cardiac Troponin I (cTNI), NT proBrain Natriuretic Peptide (NT-proBNP), Blood Natriuretic peptide (BNP), and Galectin-3.

The following endpoints are measures of safety and tolerability:

1. Complete Blood Count
2. Comprehensive Metabolic Panel
3. Electrocardiogram
4. Symptom logs

10.2 Endpoints: Echocardiography

Echocardiograms will be performed at each institution on the day of the eligibility screening, and every 6 months thereafter until study completion on Day 730. Studies will include 2-dimensional loops recorded as 2 beat digital video clips, M-mode measurements as well as spectral Doppler imaging per the AHA/ACC task force practice guidelines for the clinical application of echocardiography.[133] Refer to the ECHO Protocol posted on the study web page on the COG website for detailed instructions. All echocardiograms should have a clinical reading by the institutional study cardiologist, to ensure that there are no clinically significant decreases in cardiac function (resting EF < 50%, FS < 25%) or a 20% drop from an earlier test. Digital copies will be sent for central review at Boston Children's Hospital.

10.2.1 Digital Echocardiographic Imaging Handling and Transfer

Digital films will be transported from each participating site to the central coordinating center at City of Hope using standard DICOM format. Serial

echocardiograms for each patient will be performed at the same facility using the same machine whenever possible. Digital echocardiographic files will be submitted as a DICOM format electronic file on CD-ROM to the address below. The CD-ROM will be labeled with the subject's name, COG patient ID number, site, and the date of preparation of the CD-ROM. A Cardiac Imaging Submission Form will be submitted along with the CD-ROM.

[redacted]

Institutions should de-identify the echo films prior to shipping. If that's not possible, then after the CD-ROM arrives, study staff will remove any electronically embedded patient identifiers and procedure dates from the header of each image file using a program called ShowCase.

Film IDs will be assigned to each echocardiographic image, consisting of the participant ID plus the letter "A", "B", "C", "D" or "E" in random order with respect to timing. The procedure date for each echocardiogram will be tracked in a database that documents which letter was assigned. Anonymized films will be sent via CDROM for central review at Boston Children's Hospital.

10.3 Endpoints: Blood Biomarkers

10.3.1 Blood Collection and Processing

Peripheral blood will be sampled at the eligibility screening and every six months while on treatment.

Whole blood will be drawn into:

- one 6-mL lithium heparin-containing green top, and
- two EDTA-containing lavender-top (one 4-mL and one 6-mL) vacutainer tubes.

All tubes should be gently inverted 8-10 times after being drawn. All tubes will require processing at the site and should be transported immediately after blood draw to the specimen processing center. An overview of specimen processing and handling is provided below.

10.3.2 Handling the Green-Top Tube

The **6 mL green-top tube** should be inverted 8-10 times to gently mix the blood in lithium heparin and immediately transported to the CLIA-approved chemistry laboratory at the local site for determination of creatinine, and liver function (bilirubin, AST/ALT) per institutional protocols. Results will be recorded on the Site Lab Values Form and digitally submitted through a secure study website based at City of Hope.

10.3.3 Processing and Handling the Lavender-Top Tubes

The **4 mL lavender-top tube** should be inverted 8-10 times to gently mix the blood in EDTA and immediately transported to the CLIA-approved hematology laboratory at the local site for determination of a complete blood count (CBC) per standard protocol. Results will be recorded on the Site Lab Values Form and digitally submitted through a secure website based at City of Hope.

The **6 mL lavender-top tube** should be inverted 8-10 times to gently mix the blood in EDTA. Plasma samples will be prepared by spinning the tube in a balanced centrifuge at 1200 x g for 10 min. Plasma is aliquoted into up to 5 study-labeled cryovials with 0.5 mL in the first aliquot, 0.7 mL in the second, 0.2 mL in the third, 0.2 mL in the fourth, and any remaining plasma (up to 1 mL) in the fifth aliquot. All aliquots will be placed in a -20°C freezer within 2 hours of collection time. All aliquots will be labeled with COG Patient ID number, date of blood draw, blood draw tube ("EDTA"), and plasma aliquot number (1-5) using permanent marker or a laser printer on cryo-labels.

At the eligibility screening only: the 6 mL EDTA tube with remaining contents (after removal of plasma) will also be labeled with COG Patient ID and date of blood draw and stored in a -20°C freezer until shipment. All plasma aliquots and the EDTA tube will be shipped on dry ice to the address below, accompanied by a study-specific Specimen Submission Form. If not shipped on the day of collection, blood can be stored in a -20°C freezer until shipment. Specimens may also be batched for convenience. Blood should be shipped overnight to City of Hope Monday through Thursday only (no holiday shipments). [redacted] to receive a FedEx label for the shipment. Do NOT use the COG FedEx account.

Ship to:

[redacted]

10.3.4 Specimen Disposition after Receipt at City of Hope.

Tube #	Volume	Tests	Tube type	Storage	City of Hope ships to:
1	0.5	B-type natriuretic peptide (BNP)	4 mL white-top transport tube	-20°C (until shipping)	External Lab
2	0.7	Cardiac Troponin I (cTNI) and proBrain Natriuretic Peptide (NT-ProBNP)	4 mL white-top transport tube	-20°C	Assayed at City of Hope (RAMP tests)
3	0.2	Galectin-3	1.7 mL O-ring tube	-80°C	External Lab
4	0.2	Storage (in case of shipping or testing failure)	1.7 mL O-ring tube	-80°C	Stored at City of Hope
5	**Remaining volume**	Storage (in case of shipping or testing failure)	4 mL white-top transport tube	-80°C	Stored at City of Hope
Blood remaining in the EDTA tube will be stored at -80°C upon arrival and will be used to extract DNA for pharmacogenetics studies					

10.3.5 Storage of Blood Samples

All plasma aliquots and the extracted DNA (if applicable) will be transferred to City of Hope Outcomes Research Laboratory, where they will be entered into a specimen tracking database and stored at -80°C until assays are performed.

10.3.6 Cardiac Blood Biomarkers

A description of blood biomarkers can be found in Section 2.4.1. The following blood biomarkers will be measured:

1. Cardiac troponin (cTnI)
2. B-type natriuretic peptide (BNP)
3. NT proBrain Natriuretic Peptide (NT-proBNP)
4. Galectin-3

10.4 Pharmacogenetics Measures

The remaining blood from the 6 mL lavender-top tube will be processed for DNA to allow for analyses of SNPs including the β_1-Adr. receptor, β_2-Adr. receptor, α_{2c}-Adr. receptor and NE transporter gene polymorphisms outlined in Section 2.5.

10.5 Specimen Storage

Unused biological materials will only be stored for the purposes specifically outlined in this protocol. Once the study is complete, all unused specimens will be destroyed.

10.6 Other Study Procedures

10.6.1 Measurement of Blood Pressure, Heart Rate, Body Weight and Height

Blood pressure, heart rate, body height and weight will be measured prior to enrollment, as well as at each subsequent clinic visit whenever possible. The same method should be used to measure blood pressure throughout the study. All measurements should be made on the same extremity using appropriate cuff size and equipment. Diastolic blood pressure will be measured at the disappearance of

Kortkoff sounds – Phase V. If possible, measurements will be taken by the same staff member at each visit.

Sitting/supine blood pressure and heart rate should be measured after the subject has been sitting quietly for at least 5 minutes. Body height and weight should be measured without shoes, using the same equipment at each visit whenever possible.

10.6.2 Electrocardiogram (ECG)

A 12-lead ECG will be performed during the eligibility screening, prior to each dose escalation (Day 14 and Day 42). A sample of each ECG will be clearly labeled with COG patient ID number, protocol number and date recorded. Any clinically significant ECG findings present at the eligibility screening that would result in exclusion from study (i.e. sustained or symptomatic ventricular dysrhythmias uncontrolled with drug therapy or implantable device, significant conduction defects: second or third degree atrio-ventricular block or sick sinus syndrome) will be recorded in the Eligibility Screening Worksheet. Any subsequent clinically significant ECG changes occurring after the start of study medication should be documented as an adverse event.

10.7 Questionnaire Data

Self-reported and CRA/CRN administered questionnaires will be used to obtain baseline data on demographics, family history, and other CV risk factors, as well as to assess patient reported symptoms during the course of the study. All these questionnaires will be designed as scannable forms, using the Teleform software, such that the data entry is efficient and accurate and exported into an electronic database effortlessly.

Patient demographics, family history and baseline CV risk factors:
Standardized questionnaires will be used to obtain the following prior to study entry (see study web page):

- Demographics and Medical History Form
- Family History Form

The salient domains captured by these questionnaires include date of birth, gender, race/ethnicity, socioeconomic status, and both familial and environmental CV risk factors. These questionnaires will be administered at the time of initial enrollment.

Clinical Data Regarding Prior Cancer Diagnosis and Treatment:
The following information will be obtained from medical records using a standardized data abstraction form (the Cancer Treatment History Form): date of diagnosis, stage of disease (if applicable), data elements regarding chemotherapy including dates, protocols/regimens, cumulative doses of therapeutic agents per square meter; and data regarding radiation therapy including dates, total lifetime dose, field, fractions, dose per fraction. Institutional radiation oncology summary report will be obtained whenever possible.

Patient Reported Symptoms and Adherence to the Intervention Agent:
Health related quality of life will be assessed at baseline and every 6 months during the two-year treatment period (Quality of Life Form and Cardiac Health Questionnaire). The health subscales of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) is a component of the Quality of Life questionnaire and will be administered to all study participants to assess general and physical health as well as vitality. The

questionnaire has been used in various English-speaking populations ranging from 13 to 74 years of age, representing a wide spectrum of health states (well to seriously ill). The questionnaire has consistently shown strong evidence of internal consistency, stability, convergent and discriminant validity and has been successfully administered in a similar population of childhood cancer survivors evaluated for asymptomatic cardiac dysfunction following anthracycline therapy.[38,134] Anticipated time to complete HRQL questionnaires is 10 minutes.

Pill counts will be performed to determine adherence to the prescribed intervention using the Adherence Tracking Form. Patient compliance will be assessed by recording the amount of the study drug remaining in returned bottles. Patients will be considered non-compliant if they received < 80% or > 120% of the cumulative prescribed dose for two consecutive periods. Similar cutoffs have been used to determine compliance to study medication in pediatric oncology[62,63] and non-oncology[55] randomized cardiac intervention studies. If a patient is found to be < 50% compliant during any 90 day period, they will be removed from the protocol therapy due to non-compliance. Patients should make every attempt to complete the protocol as specified. Investigators should encourage patients to comply with the protocol and return for all scheduled visits.

Pill counts will occur on Days 14, 42, 90, 180, 270, 365, 455, 540, 630, and 730 (see Section 7.1). On days that coincide with scheduled clinic visits (0, 14, 42, 90, 180, 365, 540, and 730), pill counts will occur in clinic. For non-clinic time-points (270, 455, 630), participants will report pill counts via phone interview. Pill counts for these time points will also be verified at the next in-person study visit.

Compliance will be calculated separately for each bottle of blinded study medication as follows:

$$\frac{\text{\# of tablets dispensed} - \text{number of tablets returned}}{\text{\# of tablets prescribed per day X \# of days since last visit}} \quad \text{X } 100$$

A Symptom Log will be completed by patient interview on Days 0, 14, 42, 90, 180, 270, 365, 455, 540, 630, and 730 (see Section 7.1). On days that coincide with scheduled clinic visits (0, 14, 42, 90, 180, 365, 540, 730), the symptom log will be administered in clinic. During non-clinic time-points (270, 455, 630), assessment will be completed via phone interview.

11.0 DATA COLLECTION FORMS AND SUBMISSION SCHEDULE

Specific patient-administered forms to be used and the timing that they will be submitted are outlined in Section 10.7. In addition, the CRA/CRN will be responsible for filling out the following forms. (All forms are on the ALTE1621 web page on the COG website.)

11.1 Eligibility Screening, Registration and Enrollment

The screening interview and visit will take place prior to study enrollment. Once the patient is considered eligible for the study, the CRA/CRN will register and enroll through CTSU OPEN (as explained in Section 3.1) and all subsequent data will go directly to the coordinating center at City of Hope.

11.2 Cardiac Imaging and Specimen Submission Forms

The CRA/CRN will fill out the Cardiac Imaging Submission Form to accompany submission of the baseline and semi-annual screening echocardiograms. Scheduling of these imaging tests is outlined in Section 10.2.

11.3 Cardiac Event Form

The CRA/CRN will fill out the Cardiac Event Form should a subject have a deterioration in cardiac function while on study. Should a cardiac event be confirmed, the subject will be withdrawn from protocol therapy as outlined in Section 8.1.

11.4 Other Event Form

The CRA/CRN will fill out the Other Event Form should a subject require inpatient or outpatient procedure that could be potentially related to protocol while on trial. Only for specific events outlined in Section 8.1 will the subject necessitate withdrawal from protocol therapy.

11.5 Treatment Interruptions

The CRA/CRN will fill out a Treatment Withholding Form should a subject report an interruption for any reason while on trial. The patient-reported reason and both hold and restart dates will be recorded. If the subject voluntarily chooses to stop protocol therapy, then a Study End Form will be used instead. However, if the subject chooses to continue on protocol therapy, then the Treatment Withholding Form will be submitted. If a patient is off study medication for more than 90 consecutive days, then they will go off protocol therapy. In that case, the CRA/CRN will submit both Treatment Withholding and Study End Forms.

11.6 Study End Form

The CRA/CRN will fill out the Study End Form at the time the subject goes off protocol therapy, even if they complete the full treatment course. This form records whether or not the subject completed the trial per protocol, voluntarily withdrew, or was withdrawn for another reason. For voluntary withdrawals, subjects will be asked to clarify if it was due to intolerable side effects of treatment or if it was due to another reason.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., v5.02 and all subsequent iterations prior to version 6.0).

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

13.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

13.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or***
- ***the drug package insert.***

13.2.1 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

13.2.2 Second Malignancy

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

13.3 Reporting of Adverse Events for Commercial Agents - via CTEP-AERS

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://eapps-ctep.nci.nih.gov/ctepaers

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

13.4 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the City of Hope case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Form. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade ≥ 2 AEs that can be attributed *probably or definitely* to the study drug in either study arm.

For all Grade ≥ 3 toxicities that can be attributed *probably or definitely* to the study drug in either study arm, the patient will be unblinded and taken off protocol therapy. (See Section 5.0 for emergency unblinding.)

A City of Hope Adverse Event (AE) collection form will be submitted by study personnel on Days 180, 365, 540, and 730.

13.5 Syndrome Reporting

Unless otherwise specified in this protocol, syndromes should be reported as a single event using the CTCAE term for the composite syndrome, and not as the individual events that make up the syndrome. For example, Tumor Lysis Syndrome should be reported under the composite definition rather than reporting the component events (hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia) separately.

14.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection Documents*". A submission schedule is included.

14.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

14.2 Data Safety and Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released

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APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov..

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Protocol Specific Requirements for Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;*
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

APPENDIX II: INTERIM MONITORING

ACTIVATION PROTOCOL:

Plans for Interim Monitoring for Toxicity

Table s1: One-sided interim stopping boundaries for interaction test for treatment effect, concluding carvedilol superiority if the conditions are met.

		Superiority Bounds (O'Brien-Fleming boundaries)	
Analysis	After N completes study	Reject H0 if test statistic greater than O-F bound	Reject H0 if test statistic p is less than nominal alpha
Interim #1	83	3.7103	0.0001
Interim #2	166	2.5114	0.0060
Final	250	1.9930	0.0231

In addition to efficacy assessment, two blinded interim analyses will be performed to evaluate futility - after approximately 33% and 66% of patients have been accrued and evaluated. Our futility boundaries are calculated by using the Lan-DeMets spending approach applied to the O'Brien-Fleming boundaries as applied to beta. If the test statistic does not fall within the O'Brien-Fleming boundaries as specified in Table below, the DSMC will continue to randomize subjects. However, if the test statistic falls outside of the O'Brien-Fleming boundaries at an interim analysis, the DSMC will discuss whether the patients are receiving no benefit from carvedilol and consider discontinuing randomization. The O'Brien-Fleming boundaries in the table below are considered "non-binding", meaning that the DSMC has the option, but not the obligation, of halting the study if the futility boundaries are crossed.

Table s2: One-sided interim stopping boundaries for interaction test for treatment effect, concluding that the carvedilol arm shows no improvement over the placebo arm.

		Futility Bounds (O'Brien-Fleming boundaries)	
Analysis	After N completes study	Reject H1 if test statistic less than O-F bound	Reject H1 if test statistic p is greater than nominal alpha
Interim #1	83	-0.2361	0.5933
Interim #2	166	1.1704	0.1209
Final	250	1.9930	0.0231

In both of the interim analyses and the final analysis, the intent-to-treat data set will be the primary analysis group. In the interim analyses, the data will be analyzed with consideration of missing data. In each interim analysis, we will examine the effects of both pattern mixture models and selection models to assess the validity of the main GEE model estimates and particularly the treatment effect. To stop the trial, it will not be sufficient merely to show a treatment effect in the main GEE model. We will also look for supporting evidence such as a corresponding robustness of effect in the unstructured mean model, the pattern mixture models and the selection models.

WITH AMENDMENT #4

Table s3: One-sided interim stopping boundaries for interaction test for treatment effect, concluding that the carvedilol arm shows no improvement over the placebo arm.

		Futility Bounds (O'Brien-Fleming boundaries)	
Analysis	After N completes study	Reject H1 if test statistic less than O-F bound	Reject H1 if test statistic p is greater than nominal
Interim #1	87	1.502	0.067
Final	114	1.960	0.025

In the interim analyses and the final analysis, the intent-to-treat data set will be the primary analysis group. In the interim analysis, the data will be analyzed with consideration of missing data. To stop the trial, it will not be sufficient merely to show a treatment effect in the main GEE model. We will also look for supporting evidence such as a corresponding robustness of effect in the unstructured mean model.

APPENDIX III: YOUTH INFORMATION SHEET

INFORMATION SHEET REGARDING RESEARCH STUDY ALTE1621
(for teens from 14 to 17 years of age)

A Study of Medication and Heart Health in People Who Had Cancer Treatment in Childhood

1. We have been talking with you about the side effects of cancer treatment with drugs that contain anthracycline such as Doxorubicin, Daunorubicin, Idarubicin, Mitoxantrone, or Epirubicin. One of these side effects is weakening of the heart.

2. We are asking you to take part in a research study because you received anthracycline treatment as a child. This study will look to see if taking the medication carvedilol has any effect on weakening of the heart. The study will also try to learn more about the safety and side effects of carvedilol.

3. Teens that are part of this study will be given pills to take each day for about two years. The pills may be carvedilol (real medication) or placebo (fake medication). This study is called a randomized study, because you will be randomly assigned to get carvedilol or placebo. This is like flipping a coin and saying, "Heads means I get carvedilol, and tails means I get placebo," except that a computer decides which you will take. Neither you nor your doctor makes this decision or knows which type of pills you are given.

4. Teens that are part of this study will have some study tests that would be part of regular care and other tests that require additional visits to the doctor. There will be two different tests to check how well your heart is functioning throughout the study: an echocardiogram (that uses sound waves to create a visual picture of the heart) and an electrocardiogram (that shows the patterns of the heart as it beats). Every six months throughout the study, we will ask questions about your background, past medical history and how you are feeling, emotionally and physically. This should take about 10 minutes to complete each time.

5. As part of this study, you will have some blood taken (about 3 teaspoonfuls) before taking the study drug and every six months for a total of 5 times. The purpose of the blood draw is to look at blood cell counts, chemistry tests and cardiac biomarkers (chemicals in the body associated with how the heart is working). During the first blood draw, we will save some leftover blood to look at how your DNA (genetic material in your body) responds to the study drug.

6. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that if you are assigned to get carvedilol treatment it may prevent further damage to your heart from your past anthracycline chemotherapy. If you are assigned to placebo treatment, you are not expected to benefit. We expect the information learned from this study will help other patients in the future, but we don't know for sure if there is any benefit to you of being part of this study.

7. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." There is a risk that you will have bad effects from carvedilol or even the placebo. The more common side effects from carvedilol include dizziness and tiredness. For the blood draws, you may have pain, bruising, or infection at the site of the needle stick for blood draws. Another risk is worry or concern answering study questions. Other things may happen to you that we don't yet know about.

8. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments that your doctor can tell you about. Make sure to ask your doctors any questions that you have.